

941.634

PATENT SPECIFICATION

NO DRAWINGS

941.634



Date of Application and filing Complete Specification: Oct. 16, 1961.

No. 37014/61.

Application made in United States of America (No. 69557) on Nov. 16, 1960.

Two Applications made in United States of America (Nos. 114,621 and 114,625) on June 5, 1961.

Complete Specification Published: Nov. 13, 1963.

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Index at acceptance:—Class C2, U (2, 3, 4A2, 4B1, 4B2, 4C1, 4C2, 4C4, 4C5, 4D).

International Classification:—C 07 c.

COMPLETE SPECIFICATION

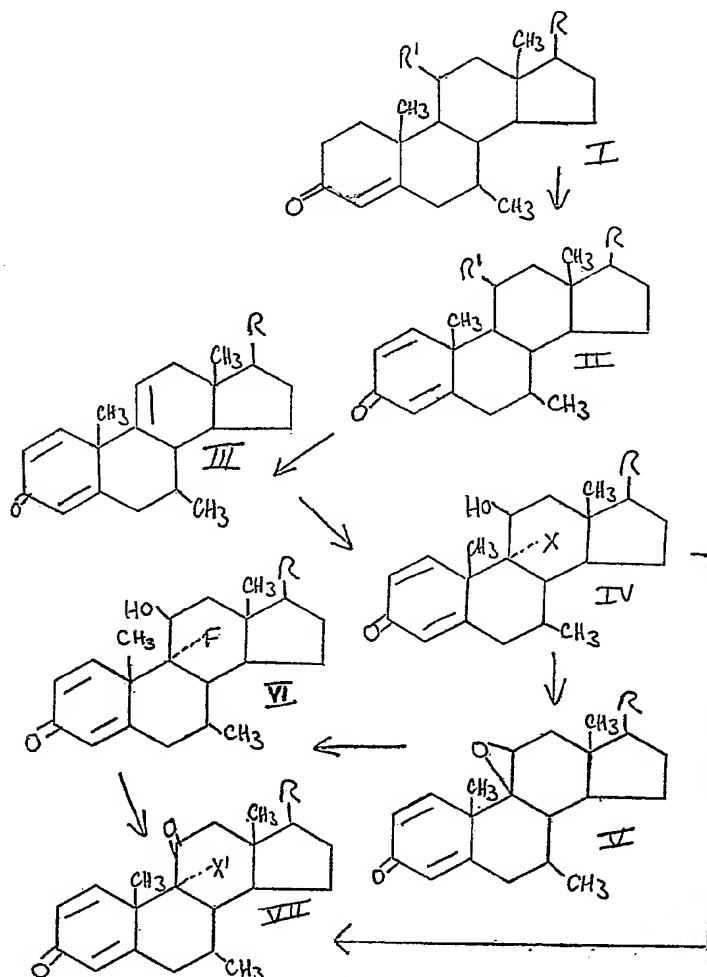
Improvements in or relating to Steroids and the manufacture thereof

We, THE UPJOHN COMPANY, a corporation organised and existing under the laws of the State of Delaware, United States of America, of 301 Henrietta Street, Kalamazoo, State of Michigan, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to certain novel steroid compounds, more particularly to certain Δ^1 -7-methyltestosterones, to certain 7-methyl-19-nortestosterones, and to processes for the production of the aforesaid compounds.

The Δ^1 -7-methyltestosterones which compounds form part of the present invention, and processes for the production thereof, are illustratively represented by the following formulae in Reaction Scheme A:

Reaction Scheme A



wherein R is β -hydroxy, β -hydroxy-17 α -methyl, β -acyloxy-17 α -methyl or β -acyloxy, R¹ is hydroxy (α and β), α -acyloxy, hydrogen, a 9(11)-double bond, or keto, the acyl radical of the acyloxy group in each instance being that of an organic carboxylic acid, preferably a hydrocarbon carboxylic acid containing from one to twelve carbon atoms, inclusive, and X is chlorine, bromine or iodine and X¹ is fluorine, chlorine, bromine or iodine. In the above formulae, the 7-methyl group represents both the alpha and beta stereoisomers and the mixture thereof.

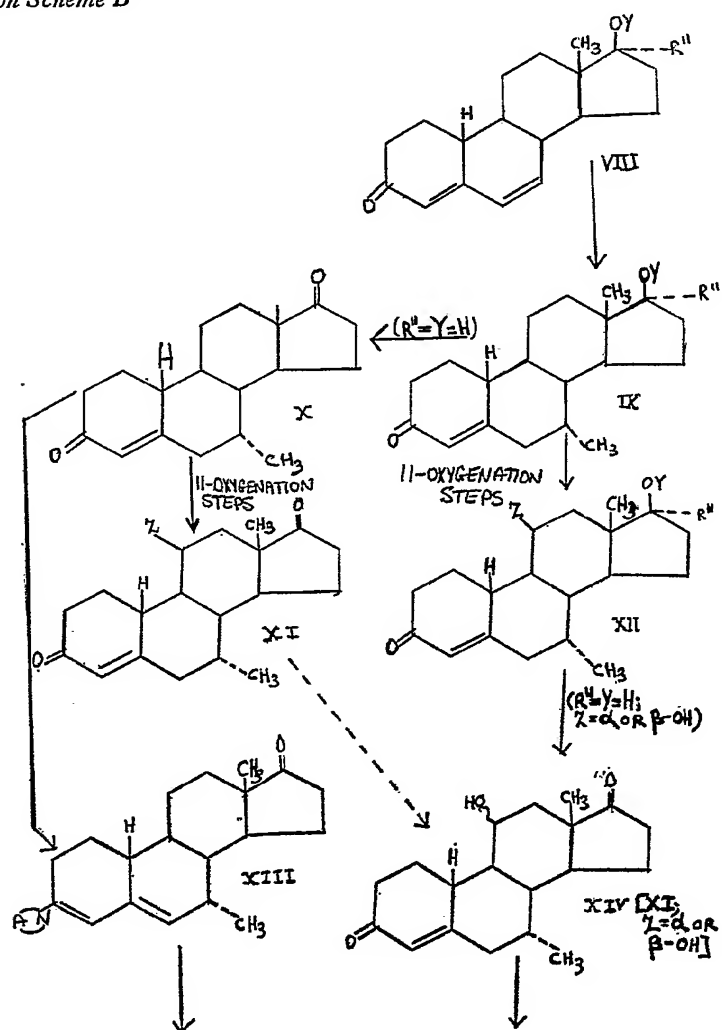
The process of the instant invention as set forth in Reaction Scheme A above comprises converting a 7-methyltestosterone (I) to the corresponding 1-dehydro derivative by methods well-known in the art, for example, by treatment with selenium dioxide using the procedure described by Meystre et al., *Helv. Chim. Acta.* 39 734 (1956), or by treatment with a 1-dehydrogenating micro-organism, for example, of the genus *Septomyxa*, using, for example, the procedure described in British Patent Specification No. 853,981. The 1-dehydro derivatives (II) so produced can then be converted to other 1-dehydro-7-methyltestosterones, e.g., by dehydrating Δ^1 -7-methyl-11 β -hydroxytestosterone or 17-acylate and Δ^1 -7,17-dimethyl-11 β -hydroxytestosterone or 17-acylate to produce Δ^1 -7-methyl-9(11)-dehydrotestosterone or 17-acylate and Δ^1 -7,17-dimethyl-9(11)-dehydrotestosterone or 17-acylate (III); treating 7-methyl-1,9(11)-dehydrotestosterone, a 17-ester thereof, 7,17-dimethyl-1,9(11)-dehydrotestosterone or a 17-ester thereof, with a hypohalous acid to obtain a Δ^1 -7-methyl-9 α -halo-11 β -hydroxy-

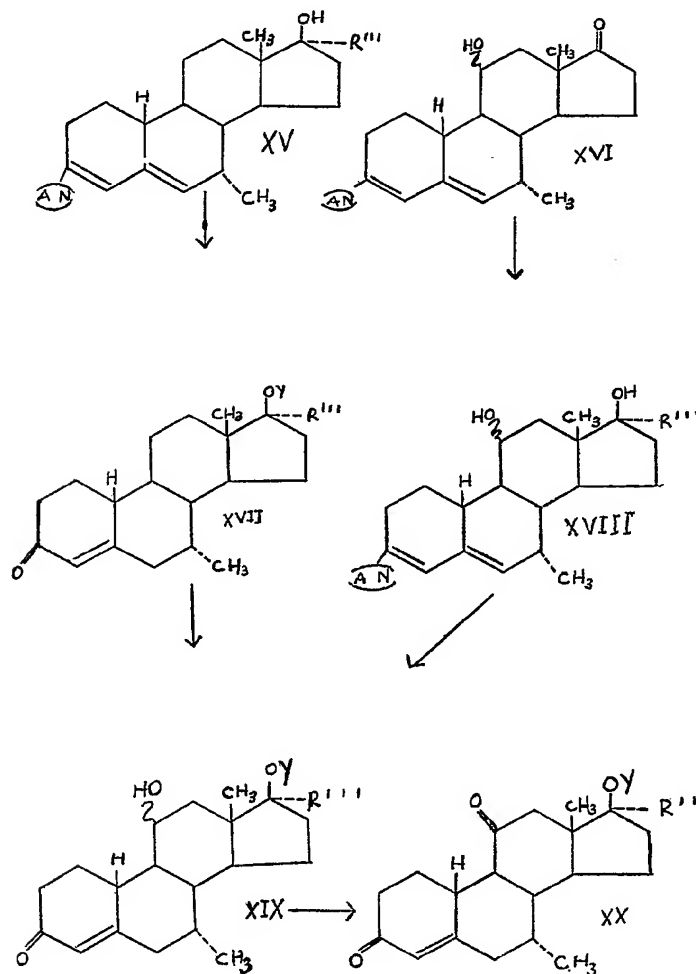
testosterone, 17-ester and Δ^1 -7,17-dimethyl-9 α -halo-11 β -hydroxytestosterone or 17-ester, respectively (IV); treating the thus-produced Δ^1 -7-methyl-9 α -halo-11 β -hydroxytestosterone, 17-ester thereof, Δ^1 -7,17-dimethyl-9 α -halo-11 β -hydroxytestosterone, or 17-ester thereof, with a weak base, e.g., potassium or sodium hydroxide in slight excess so as to produce a medium of pH 8 to 10, or potassium or sodium acetate, to obtain Δ^1 -7-methyl-9 β ,11 β -epoxytestosterone, a 17-ester thereof, Δ^1 -7,17-dimethyl-9 β ,11 β -epoxytestosterone, and 17-ester thereof, respectively (V); and reacting the thus-produced Δ^1 -7-methyl-9 β ,11 β -epoxytestosterone, 17-ester thereof; Δ^1 -7,17-dimethyl-9 β ,11 β -epoxytestosterone, or 17-ester thereof with hydrofluoric acid to obtain Δ^1 -7-methyl-9 α -fluoro-11 β -hydroxytestosterone, 17-ester thereof, Δ^1 -7,17-dimethyl-9 α -fluoro-11 β -hydroxytestosterone, and 17-ester thereof, respectively (VI). After each of the above steps, the 17-ester group, when present, can be hydrolyzed with acid in the case of IV or with base, if desired, to produce the corresponding free 17-hydroxy compound. Oxidation of a Δ^1 -7-methyl-9 α -halo-11 β -hydroxytestosterone (IV or VI) with chromic acid produces the corresponding Δ^1 -7-methyl-9 α -halo-11-ketotestosterone (VII). The 17-acylate group, when present, can be hydrolyzed with alkali-metal base to produce the corresponding Δ^1 -7-methyl-9 α -halo-11-ketotestosterone. Δ^1 -7-methyl-9 α -halo-11-ketotestosterone 17-acylates can also be hydrolyzed in alcoholic acid solutions to give the corresponding Δ^1 -7-methyl-9 α -halo-11-ketotestosterone.

A 17-acylate group can be introduced into any of the above compounds having a 17-hydroxy group, by techniques well known in the art. If there is also present a 17-methyl group, more vigorous esterification techniques are required, as is known in the art.

The 7-methyl-19-nortosterones, which form part of the present invention, and processes for the production thereof, are illustratively represented by the following formulae in Reaction Scheme B:

Reaction Scheme B





wherein R^{11} is hydrogen or lower-alkyl containing from 1 to 4 carbon atoms, inclusive, R^{111} is a lower aliphatic hydrocarbon radical containing from 1 to 4 carbon atoms, inclusive, Z is hydrogen, keto, hydroxy (α and β), or α -acyloxy, wherein the acyl of the acyloxy radical is that of an organic carboxylic acid preferably a hydrocarbon carboxylic acid as hereinbefore defined, Y is hydrogen or the acyl radical of an organic carboxylic acid, preferably a hydrocarbon carboxylic acid as hereinbefore defined, and A is an alkylene group which, together with the attached nitrogen atom, forms a ring containing from 5 to 6 members, inclusive, and which preferably contains less than 9 carbon atoms.

The term "lower aliphatic hydrocarbon radical containing from 1 to 4 carbon atoms, inclusive" means a saturated or unsaturated 1 to 4 carbon atom aliphatic hydrocarbon radical such as alkyl, for example, methyl, ethyl, propyl, butyl, and isomeric forms thereof, alkenyl, for example, vinyl, propenyl, butenyl and isomeric forms thereof, and alkynyl, for example, ethynyl, propynyl, butynyl, and isomeric forms thereof.

The organic carboxylic acids, from which the acylates of the present invention are derived, include saturated and unsaturated aliphatic acids and aromatic acids such as acetic, propionic, butyric, isobutyric, tert-butylacetic, valeric, isovaleric, caproic, caprylic, decanoic, dodecanoic, acrylic, crotonic, hexynoic, heptynoic, octynoic, cyclobutanecarboxylic, cyclopentanecarboxylic, cyclopentenecarboxylic, cyclohexanecarboxylic, dimethylcyclohexanecarboxylic, benzoic, toluic, naphthoic, ethylbenzoic, phenylacetic, naphthaleneacetic, phenylvaleric, cinnamic, phenylpropionic, phenylpropionic, p-hexyloxyphenylpropionic acid, p-butyloxyphenylpropionic acid, and like p-alkoxyphenylalkanoic acids.

The process of the invention as set forth in Reaction Scheme B above comprises: treating a 6-dehydro-19-nor-testosterone (VIII) with a methyl Grignard reagent in the presence of an agent such as a cuprous halide, preferably cuprous chloride or cuprous bromide which suppresses 1,2- addition of the Grignard reagent [Kharasch and Reinmuth "Grignard reactions of non-metallic substances" page 219, Prentice Hall 1954] to produce a 7 α -methyl-19-nortestosterone (IX). The 7 α -methyl-19-nortestosterone (IX) so produced can then be converted to other 7 α -methyl-19-nortestosterones. For example the compound (IX) can be hydroxylated in the 11-position, illustratively by treatment with an 11 α -hydroxylating microorganism using the procedures described in British Patent Specification No. 724,094 to yield the corresponding 11 α -hydroxy compound (XII; Z = α -OH), or by treatment with an 11 β -hydroxylating microorganism using procedures such as that described in British Patent Specification No. 724,094 to yield the corresponding 11 β -hydroxy compound (XII; Z = β -hydroxy). The 11-hydroxy compounds so obtained can be oxidised, for example, using chromic acid, sodium dichromate, potassium dichromate and the like, to yield the corresponding 11-keto compounds (XII; Z = keto). In the case where R¹¹ and Y = H in the 11-hydroxy compound (XII; Z = α or β -OH) such oxidation will also result in oxidation at the 17-position to give the corresponding 11,17-diketo compound.

The compound (IX; R¹¹ = Y = H) can also be oxidised, for example, with chromic acid or like oxidising agents using procedures known in the art, to obtain the corresponding 17-keto compound (X). Compound (X) so obtained can be converted to the corresponding 11 α - or 11 β -hydroxy compounds (XI; Z = α or β -OH) using the procedures described above, and the resulting 11-hydroxy compounds can be oxidized to the corresponding 11-keto compound (XI; Z = keto) using the oxidation procedures described above.

The compound (X) can also be converted to the 3-enamine (XIII), the 3-enamine (XIII) treated with an appropriate alkylating agent such as the appropriate Grignard reagent, alkyl or alkenyl lithium compound or alkali metal alkyne derivative to obtain the compound XV, and the latter compound hydrolyzed using neutral, acidic or alkaline aqueous reaction conditions, to the corresponding 17-alkylated-7-methyl-19-nortestosterone (XVII; Y = H). The 17-hydroxy group in the compound (XVII; Y = H) so obtained can be acylated, if desired, using acylating conditions known in the art, to yield the corresponding 17-acyloxy compound (XVII; Y = Ac). The compound (XVII; Y = H or Ac) can then be subjected to 11-hydroxylation using the procedures described above to obtain the corresponding 11 α - and 11 β -hydroxy compounds (XIX; Y = H) which can then be converted to the corresponding 11 α ,17-diacyloxy compounds or 11 β -hydroxy-17-acyloxy compounds by acylation using procedures well-known in the art. The 11-hydroxy compounds (XIX) can also be oxidized to the corresponding 11-keto compounds (XX) using oxidation procedures such as those described above.

In an alternative synthesis of the compounds (XIX), the compounds (XIV) obtained by Oppenauer oxidation of the compound (XII; R¹¹ = Y = H, Z = α - or β -OH) or the compound (XI; Z = α or β -OH) is converted to the corresponding 3-enamine (XVI) and the latter is treated with an alkylating agent such as those described above to obtain the 3-enamine of the corresponding 17-alkylated-11-hydroxy-7 α -methyl-19-nortestosterone (XVIII). The latter compound is then hydrolyzed using the conditions hereinbefore described to obtain the compound (XIX; Y = H).

It is an object of this invention to provide Δ^1 -7-methyltestosterones (IIa—VII) and a process for their production. It is a particular object of this invention to provide 1-dehydro-7-methyltestosterone, 1-dehydro-7-methyl-11 β -hydroxytestosterone, 1-dehydro-7,17-dimethyltestosterone, 1-dehydro-7,17-dimethyl-11 β -hydroxytestosterone, 1-dehydro-7-methyl-9 α -fluoro-11 β -hydroxytestosterone, and 1-dehydro-7,17-dimethyl-9 α -fluoro-11 β -hydroxytestosterone, and the 17-esters thereof, especially those of hydrocarbon carboxylic acids containing from one to twelve carbon atoms, inclusive.

It is a further object of this invention to provide 7-methyl-19-nortestosterones (IX, X, XI, XII, XIV, XVII, XIX and XX) and a process for their production. It is a particular object of this invention to provide 7-methyl-19-nortestosterone and the 17-esters thereof, 7-methyl-19-norandrostene-3,17-dione, 7-methyl-17-ethynyl-19-nortestosterone and the 17-esters thereof, 17-ethyl-7-methyl-19-nortestosterone and the 17-esters thereof, and 7,17-dimethyl-19-nortestosterone and the 17-esters thereof.

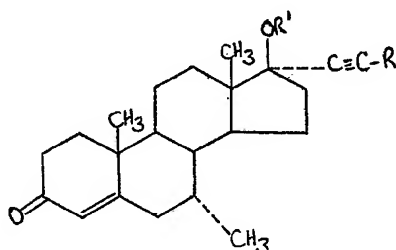
The 1-dehydro-7-methyltestosterones of the present invention (II—VII) have androgenic and anabolic activity of improved therapeutic ratio. Compounds II, and VI, wherein R¹ is hydrogen and R is β -hydroxy, β -acyloxy or β -hydroxy- α -methyl, are particularly valuable in this respect. The compounds (II—VII) also possess antiestro-

genic, gonadotropin inhibiting activity, progestational, growth-promoting and central nervous system regulating activities making them of value in medical and veterinary practice.

The 7-methyl-19-nortestosterones of the present invention (IX, X, XI, XII, XIV, XVII, XIX and XX) possess anabolic and androgenic activity with an improved potency and improved therapeutic ratio of anabolic to androgenic activity. They also possess antiestrogenic, gonadotropin inhibiting, progestational, growth-promoting, anti-fertility and central nervous system depressant activity. The compound 7 α -methyl-17 α -ethynyl-19-nortestosterone is of particular interest since it possesses greater activity as an anti-fertility agent but lower activity as a progestational agent than the closely related known compound 17 α -ethynyl-19-nortestosterone.

In addition, the 7 α -methyl-19-nortestosterones (IX—XX) of the invention are intermediates in the preparation of the corresponding 7 α -methylestrones and 7 α -methylestradiols which latter compounds possess activity as gonadotropin inhibitors, anti-fertility agents, and blood cholesterol lowering agents of improved therapeutic ratio. Thus the 7 α -methyl-19-nortestosterones of the invention can be dehydrogenated, for example, using *Septomyxa affinis* and like dehydrogenating microorganisms, to yield the corresponding 7 α -methylestrones and 7 α -methylestradiols.

It is a further object of this invention to prepare compounds represented by the following formula:



(XXI)

wherein R is hydrogen, methyl or ethyl, and R¹ is hydrogen or acyl wherein the acyl radical is that of an organic carboxylic acid, preferably that of a hydrocarbon carboxylic acid containing from 1 to 12 carbon atoms, inclusive.

The compounds (XXI) possess anabolic and androgenic activity with an improved therapeutic ratio of anabolic to androgenic activity. They also possess antiestrogenic, gonadotropin-inhibiting, progestational, growth-promoting, antifertility, and central nervous system depressant activity which make them useful in medical and veterinary practice.

The compounds of formula (XXI) are also useful as intermediates in the preparation of the corresponding 7 α -methyl-17 α -alkyltestosterones and the corresponding 17-acylates thereof. Thus the compounds of the invention can be hydrogenated in the presence of a hydrogenation catalyst such as palladium-on-charcoal whereby the 17 α -alkynyl group is converted to the corresponding 17 α -alkyl group. The 7 α -methyl-17 α -alkyltestosterones and 17-acylates thereof so obtained are themselves active as anabolic and androgenic agents with an improved therapeutic ratio of anabolic to androgenic activity. They also possess anti-estrogenic, gonadotropin-inhibiting, progestational, growth-promoting, antifertility, and central nervous system depressant activity which makes them useful in medical and veterinary practice.

The compounds of the formula (XXI) can be prepared in a convenient manner using the following procedure. Oxidation of 7 α -methyltestosterone [J. Allan Campbell and J. C. Babcock, J. Am. Chem. Soc., 81, 4069, (1959)] with oxidizing agents such as chromic acid, sodium dichromate or potassium dichromate, using procedures known in the art yields 7 α -methylandrostene-3,17-dione. The latter compound is then converted to the corresponding 3-enamine, for example, by reaction with a secondary cyclic alkyleneamine containing from 5 to 7 ring atoms, inclusive, such as pyrrolidine, piperidine, morpholine, and C-alkyl substituted pyrrolidines, piperidines, and morpholines such as 2,4-dimethylpyrrolidine, 3-propylpiperidine, 2-methylpyrrolidine, 3,4-dimethylpyrrolidine, 3-ethylpyrrolidine, 3-isopropylpyrrolidine, 3,3-dimethylpyrrolidine, 2-methylmorpholine and 3-methylmorpholine. Pyrrolidine is the preferred amine for use in the above reaction.

Advantageously, the 3-enamine is prepared by heating the 7 α -methylandrosterone-3,17-dione and the secondary cyclic alkyl enamine together in the presence of a suitable solvent, for example, a lower alkanol such as methanol or ethanol. The desired 3-enamine generally separates from the reaction mixture and is isolated and dried for a short period before being used without further purification in the next stage of the synthesis.

The 3-enamine of 7 α -methylandrosterone-3,17-dione so obtained is then reacted with an alkali metal derivative, for example, the sodium or potassium derivative of the appropriate alkyne. The reaction is carried out preferably in the presence of an anhydrous inert solvent such as dimethylformamide, dimethylsulphoxide, and the like. The 3-enamine of 7 α -methyl-17 α -alkynyltestosterone so obtained is not generally isolated from the reaction mixture but is hydrolyzed in situ to the free 7 α -methyl-17 α -alkynyltestosterone by treatment with an aqueous solution of a base such as sodium hydroxide or potassium hydroxide, after first decomposing the reaction mixture with water or ammonium chloride.

The 7 α -methyl-17 α -alkynyltestosterone so obtained can be purified, if desired, by procedures known in the art such as by recrystallization, chromatography, and the like.

The 7 α -methyl-17 α -alkynyltestosterones (XXI) can also be prepared by reacting the 3-enamine of 7 α -methylandrosterone-3,17-dione, prepared as described above, with the appropriate alkynylmagnesium halide. The reaction is preferably carried out in the presence of a solvent such as dimethyl ether or tetrahydrofuran. Preferably, the Grignard reagent is employed in an excess of the order of 10 moles per mole of the 3-enamine. The 3-enamine of 7 α -methyl-17 α -alkynyltestosterone so obtained is generally not isolated from the reaction mixture but is hydrolyzed in situ to the free 7 α -methyl-17 α -alkynyltestosterone by the method described above.

The 17-acylates of formula (XXI) can be prepared by procedures known in the art, for example, by reacting the 7 α -methyl-17 α -alkynyltestosterone with the appropriate acid anhydride or acid halide in the presence of a tertiary organic base such as pyridine. In this manner there can be prepared 7 α -methyl-17 α -alkynyltestosterone 17-acylates wherein the acyl radical is derived from organic carboxylic acids such as acetic, propionic, butyric, isobutyric, tert-butylacetic, valeric, isovaleric, caproic, caprylic, decanoic, acrylic, crotonic, hexynoic, heptynoic, octynoic, cyclobutanecarboxylic, cyclopentanecarboxylic, cyclopentenecarboxylic, cyclohexanecarboxylic, cyclopentylpropionic, p-butoxyphenylpropionic, p-hexyloxyphenylpropionic, benzoic, toluic, naphthoic, ethylbenzoic, phenylacetic, naphthaleneacetic, phenylvaleric, cinnamic and phenylpropionic.

The compounds of this invention can be prepared and administered to mammals, birds, humans, and animals, in a wide variety of oral or parenteral dosage forms singly, or in admixture with other coating compounds. They can be administered with a pharmaceutical carrier which can be a solid material or a liquid in which the compound is dissolved, dispersed or suspended. The solid compositions can take the form of tablets, powders, capsules or pills, preferably in unit dosage forms for simple administration or precise dosages. The liquid compositions can take the form of solutions, emulsions, suspensions, syrups or elixirs. The oral forms are preferably used for the 17 α -alkylated-17 β -hydroxy compounds of this invention which possess particularly advantageous oral activity.

In carrying out the process of the present invention illustrated in Reaction Scheme A, 7-methyltestosterone (I) is converted to the corresponding 1-dehydro-7-methyltestosterones (II) by the procedures hereinbefore described. The 1-dehydro compounds (II) so obtained can be purified by procedures known in the art, for example, by recrystallization or by chromatography. Where the crude 1-dehydro compound (II) contains an appreciable amount of the unconverted starting material (I) the mixture can be separated by conversion of the latter to the corresponding 3-enamine. For example, refluxing the mixture of (I) and (II) in benzene in the presence of a secondary cyclic alkyl enamine such as pyrrolidine for several hours converts the compound (I) to its 3-enamine whereas the compound (II) does not form an enamine under such conditions. The mixture of the compound (II) and the 3-enamine of (I) can then be separated by treatment with dilute mineral acid when the 3-enamine dissolves and the compound (II) can be recovered and purified further, if necessary, for example by recrystallization.

In the next step of the process of Reaction Scheme A, a Δ^1 -7-methyl-11-hydroxytestosterone (II, R¹ = OH) is dehydrated by the process shown in the example, or by prior art procedure for dehydration of 11 α - and 11 β -hydroxy steroids, e.g., [Fieser and Fieser, "Natural Products Related to Phenanthrene", Reinhold Publishing Corporation, New York, New York, 1949, pages 408-409], to produce the corresponding 7-methyl-

1,9(11)-dehydrotestosterone (III). The compound (III) dissolved in a suitable solvent such as, for example, methylene chloride, tertiary butyl alcohol, dioxane, tertiary amyl alcohol, or acetone, is reacted with a hypohalous acid, i.e., hypochlorous, hypobromous or hypoiodous acid to produce the corresponding 1-dehydro-7-methyl-9 α -halo-11 β -hydroxytestosterone (IV).

Instead of using the free acid it is usually more convenient to produce the hypohalous acid in situ by reacting an N-haloamide or an N-haloimide with a mineral acid. N-haloamides or an N-haloimides useful in this procedure include N-chloroacetamide, N-bromoacetamide, N-chlorosuccinimide, N-bromosuccinimide and N-iodosuccinimide. The mineral acid used to liberate the hypohalous acid is usually dilute perchloric or dilute sulphuric acid. The reaction is generally carried out at temperatures between zero and thirty degrees centigrade, however, lower or higher temperatures are operative for the process. The hypohalous acid releasing agent is generally used in equimolar proportion or in slight excess, e.g., a 25 percent excess. A large excess of the hypohalous acid-releasing agent, while operative, is undesirable since the excess of hypohalous acid has a tendency to react with other positions of the molecule. The reaction period is rather short and may vary between about four to five minutes to one hour. At the end of the reaction time excess hypohalous acid is destroyed by the addition of sodium sulphite or other sulphites or hydrosulphites. The thus-produced product, a Δ^1 -7-methyl-9 α -halo-11 β -hydroxytestosterone (IV), is isolated from the reaction mixture by adding an excess of water and extracting the reaction mixture with organic solvents such as methylene chloride, chloroform, benzene, toluene, ether, ethyl acetate and hexane hydrocarbons (Skellysolve B), or by filtration. The crude product thus obtained is purified by conventional procedures such as recrystallization or chromatography, as deemed necessary.

The Δ^1 -7-methyl-9 β ,11 β -epoxytestosterones (V) are prepared by treating the appropriately substituted compound (IV) with a mild base. In this reaction the compound (IV) is dissolved in an organic solvent such as, for example, methanol, ethanol, isopropanol, dioxane, tertiary butyl alcohol, or tetrahydrofuran, and treated with a base, e.g., potassium acetate, sodium bicarbonate, or a sodium acylate, e.g., sodium acetate. If the starting material is a 17-ester of a compound (IV) sodium or potassium acetate is preferred in order to avoid simultaneous hydrolysis of such ester. Heating of the reaction mixture is preferred and the reaction time is usually between three and twelve hours. Alternatively a methanolic solution of compound (IV) is stirred at room temperature with aqueous base such as sodium hydroxide, potassium hydroxide or barium hydroxide. The base is added slowly with continuous agitation and carried only to the point at which the reaction mixture remains basic to phenolphthalein for a period of about one-half minute. The thus-obtained 1-dehydro-7-methyl-9 β ,11 β -epoxytestosterone (V) is separated from the reaction mixture by conventional means such as adding an excess of water to the reaction mixture and either filtering the thus-produced precipitate or extracting with water-immiscible solvent, e.g., ether, hexanes (Skellysolve B) pentanes, benzene, ether, ethyl acetate, chloroform, methylene chloride or carbon tetrachloride. Purification of the thus obtained compound (V) may be by conventional means such as recrystallization or chromatography.

The Δ^1 -7-methyl-9 β ,11 β -epoxytestosterones (V) are converted to Δ^1 -7-methyl-9 α -fluoro-11 β -hydroxytestosterones (VI) by reaction with 48 percent aqueous hydrofluoric acid solution in a solvent. As solvents for this reaction, methylene chloride, ethylene dichloride, chloroform or carbon tetrachloride, are used with methylene chloride and chloroform preferred. The reaction in the preferred embodiment is carried out in the presence of acid catalysts such as perchloric acid, toluenesulphonic acid, sulphuric acid, or the like. The reaction temperature is preferably from twenty to thirty degrees centigrade. The period of reaction is from one to 24 hours. Instead of aqueous hydrofluoric acid, hydrogen fluoride gas, dissolved in a chilled solution of alcohol-free chloroform or methylene chloride, preferably containing tetrahydrofuran, can be used. In this case, a chilled solution of compound (V) in a convenient solvent such as chloroform, methylene chloride or carbon tetrachloride, contained in a polyethylene bottle, is admixed with a chilled solution of gaseous hydrogen fluoride in chloroform, methylene chloride, or carbon tetrachloride solution. The stoppered bottle is then allowed to stand for a period of between one hour and 24 hours at low temperatures, e.g., between minus forty and plus ten degrees centigrade, with temperatures between zero and minus 25 degrees centigrade preferred. After the reaction is terminated, the reaction mixture obtained by either of the two methods is neutralized with an aqueous base such as aqueous sodium bicarbonate, aqueous sodium carbonate, potassium carbonate or bicarbonate, or dilute sodium or potassium hydroxide, and the thus-obtained Δ^1 -7-methyl-

9 α -fluoro-11 β -hydroxytestosterone, or ester thereof, is separated from the reaction mixture by conventional means such as extraction with water-immiscible organic solvents, for example, ether, ethyl acetate, hexanes (Skellysolve B), chloroform, carbon tetrachloride or methylene chloride. Evaporation of the extraction solvent gives the crude compound (VI) which can be purified by conventional means, e.g., recrystallization or chromatography.

In order to obtain Δ^1 -7-methyl-9 α -halo-11-ketotestosterones (VII), any one of the before-mentioned Δ^1 -7-methyl-9 α -halo-11 β -hydroxytestosterone 17-esters (IV, VI, R = acyloxy) or Δ^1 -7,17-dimethyl-9 α -halo-11 β -hydroxytestosterone (IV, VI, R = β -hydroxy- α -methyl) is oxidized preferably by chromic acid in an acidic solvent, e.g., acetic acid, acetic acid plus benzene or dilute mineral acid plus methylene chloride.

Hydrolyzing a Δ^1 -7-methyltestosterone 17-acylate (II—VII, R = acyloxy) with an alkali metal base in aqueous alcoholic solution or dilute mineral acid produces the corresponding Δ^1 -7-methyltestosterone as the free 17-alcohol.

The pure 7-stereoisomers, each free from the other, can be obtained by fractional crystallization or carbon chromatography to obtain one of the isomers and then treatment of the residual mixture of isomers with chloranil which reacts with only the 7 β -isomer leaving the 7 α -isomer unchanged, and then separating that isomer from the resulting 6-dehydro compound as shown in Example 2. The 6-dehydro-7-methyl compound resulting from the chloranil reaction can be converted back to the 7 β -methyl compound by selective hydrogenation using, for example, a palladium-on-charcoal catalyst as disclosed by Shepherd et al, J. Am. Chem. Soc. 77, 1212, 1955.

The starting materials having the general formula I and the preparation thereof are described and claimed in our British Patent Specification No. 863,661.

In carrying out the process of the present invention as illustrated in Reaction Scheme B, the starting 6-dehydro-19-nortestosterone (VIII) is reacted with an excess of a methyl Grignard reagent, for example, methyl magnesium iodide or methyl magnesium bromide, in the presence of cuprous chloride or equivalent catalyst; see "Grignard Reaction", Kharasch and Reinmuth, Prentice Hall, Inc. Publishers (1954) p. 219 for a discussion of other catalysts supra. Cuprous chloride is preferred. Various inert solvents can be employed, for example, benzene, toluene, ethylene glycol dimethyl ether, ether or tetrahydrofuran, or a mixture of any two of these solvents. The reaction temperature can vary between minus 40° C. and the boiling point of the reaction mixture. A temperature between about 0° C. and 60° C. is preferred. The Grignard reagent is preferably employed in the ratio of at least 5 moles of Grignard per mole of steroid. Methyl magnesium bromide produces the highest yield of desired product and is the preferred reagent.

Where the group Y is hydrogen in the compound (IX) so obtained said compound can be acylated to produce the corresponding 17-acyloxy compound (IX; Y = Ac). The acylation can be accomplished using methods known in the art, for example, by treatment with the appropriate acid anhydride or acid halide in the presence of a tertiary base such as pyridine.

The 7 α -methyl-19-nortestosterone (IX) can be subjected to 11-hydroxylation as follows. The compound (IX) can be subjected to the action of the enzymes of an 11 α -hydroxylating microorganism such as those of the genera *Mucorales*, *Aspergillus*, *Penicillium* and *Streptomyces* using, for example, the procedures described in British Patent Specification No. 724,094. There is thus obtained the compound (XII) wherein Z = α -hydroxy and Y = hydrogen. Alternatively, the compound (IX) can be subjected to the action of the enzymes of an 11 β -hydroxylating microorganism such as *Cunninghamella blakesleeana*, *Curvularia lunata*, *Trichothecium roseum*, and the like using procedures well known in the art, for example, that described in British Patent Specification No. 724,094. There is thus obtained the compound XII wherein Z = β -hydroxy and Y = hydrogen.

Where the group Y is acyl in the compound (IX) said group will generally be removed during the microbiological hydroxylation procedures and in order to obtain the compound (XII) wherein Y is acyl it is necessary to acylate the free 17-hydroxy group using procedures such as those described above. Such acylation will also convert the 11 α -hydroxy, when present, to the corresponding 11 α -acyloxy group.

In order to obtain the compound (XII) wherein Z is keto, the corresponding 11 α or β -hydroxy compound (XII; Z = α or β -OH and Y = Ac when R¹¹ is hydrogen) is oxidized using procedures known in the art. For example, the oxidation can be effected using chromic acid, sodium dichromate, potassium dichromate and like oxidizing agents.

The compound (IX) wherein Y and R¹¹ both represent hydrogen, i.e., 7 α -methyl-19-nortestosterone, can be oxidized to the compound (X), i.e., 7 α -methyl-19-nor-

androstene-3,17-dione, using procedures known in the art, for example, using chromic acid, sodium dichromate, potassium dichromate and like oxidizing agents.

The 7 α -methyl-19-norandrostene-3,17-dione (X) so obtained can then be converted to the corresponding 11 α -hydroxy, 11 β -hydroxy, and 11-keto compound (XI) using the procedures described above for the 11-hydroxylation of compound (IX) and the oxidation of the 11-hydroxy compounds to 11-keto.

The compound (X) can also be converted to the compounds (XVII), (XIX) and (XX) of the invention using the following procedure. The 7 α -methyl-19-norandrostene-3,17-dione (X) is first converted to the corresponding 3-enamine, for example, by reaction with a secondary cyclic alkylene amine A NH, wherein A has the significance hereinbefore defined, if desired in the presence of an acid catalyst.

The secondary cyclic alkylene amines which can be used in the above reaction include pyrrolidine, piperidine, and C-alkyl substituted pyrrolidines, and piperidines such as 2,4-dimethylpyrrolidine, 3-propylpiperidine, 2-methylpyrrolidine, 3,4-dimethylpyrrolidine, 3-ethylpyrrolidine, 3-isopropylpyrrolidine, 3,3-dimethylpyrrolidine, and other lower alkyl C-substituted pyrrolidines, and piperidines. Pyrrolidine is the preferred amine for use in the above reaction. Advantageously, the amine is employed in excess of the required molar proportion. The reaction between the compound (X) and the amine is effected in a convenient manner by heating the reactants together in the presence of a suitable solvent, for example, a lower alkanol such as methanol, ethanol, and the like. The desired 3-enamine (XIII) generally separates from the reaction mixture after concentrating the latter and allowing to cool.

The 3-enamine (XIII) so obtained is then converted to the 3-enamine of the corresponding 17-alkylated compound (XV) by reaction with the appropriate alkylating agent. For example, the 3-enamine (XIII) can be reacted with the appropriate alkyl, alkenyl, or alkynyl magnesium halide in the presence of a solvent such as dimethyl ether, tetrahydrofuran or benzene, to produce the corresponding compound (XV) wherein R¹¹ is alkyl, alkenyl, or alkynyl as hereinbefore defined. Preferably, the Grignard reagent is employed in an excess of the order of 10 moles per mole of enamine (XIII). The resulting 17-alkylated 3-enamine (XV) is generally not isolated from the reaction mixture but is hydrolyzed in situ to the corresponding 7 α -methyl-17-alkylated-19-nortestosterone (XVII) by treatment with an aqueous solution of a base such as sodium hydroxide, potassium hydroxide, and the like after first decomposing the reaction mixture with water, ammonium chloride, and the like.

Alternatively, the alkylating agent employed to convert the enamine (XIII) to the 17-alkylated compound (XV) in the case where R¹¹ is alkyl or alkenyl, can be the appropriate alkyl or alkenyl lithium compound. The reaction is conducted advantageously in the presence of an inert solvent such as ether, benzene, toluene and the like. The lithium compound is employed advantageously in excess of the stoichiometric proportion and is employed preferably in an amount of at least 1.5 moles per mole of compound (XIII). The reaction is ordinarily conducted at room temperature but may also be conducted at elevated temperatures up to the boiling point of the solvent employed. The 17-alkylated-3-enamine (XV) so formed is generally not isolated but is hydrolyzed in situ to the corresponding 3-keto compound (XVII) as hereinbefore described.

The compounds having the formula (XVII) wherein R¹¹ represents a 2 to 4 carbon atom alkynyl group can also be prepared by reacting the enamine (XIII) with an alkali metal derivative, for example, the sodium or potassium derivative of the corresponding alkyne. The reaction is carried out preferably in the presence of an inert solvent such as dimethylformamide or dimethylsulphoxide. The 17-alkynyl-3-enamine (XV) so obtained is not generally isolated from the reaction mixture but is hydrolyzed in situ as described above to obtain the desired compound (XVII).

The compound (XVII) where R¹¹ represents alkynyl or alkenyl can be hydrogenated in the presence of a suitable hydrogenation catalyst such as palladium-on-charcoal to obtain the corresponding compounds in which R¹¹ is a 2 to 4 carbon atom alkyl group.

The 7 α -methyl-17-alkylated-19-nortestosterones (XVII; Y=H) so obtained can be acylated using the procedures hereinbefore described to obtain the corresponding 17-acyloxy compounds (XVII; Y=Ac).

The compounds (XVII) can be converted to the corresponding 11 α -hydroxy and 11 β -hydroxy compounds (XIX) using the microbiological oxidation procedures hereinbefore described, and the 11 β -hydroxylated compounds (XIX) can be oxidized to the corresponding 11-keto compounds (XX) using the oxidation procedures hereinbefore described. The microbiological hydroxylations will generally result in the removal of the 17-acyl group if this is present in the starting compound (XVII). The free 17-

hydroxy group in the resulting compound (XIX; Y=H) can be reacylated if desired using the procedures described above.

The compound (XIX) wherein R^{11} represents alkynyl or alkenyl can be hydrogenated in the presence of a suitable hydrogenation catalyst such as palladium-on-charcoal to obtain the corresponding compounds in which R^{11} is a 2 to 4 carbon atom alkyl group.

In an alternative method of preparation of the compounds XIX and XX, the compound XII, wherein $R^{11}=Y=H$ and $Z=\alpha$ or β -OH, is subjected to an Oppenauer oxidation using procedures known in the art, for example, using aluminum tert-butoxide and acetone or cyclohexanone in the presence of an anhydrous organic solvent such as toluene, benzene, petroleum ether, dioxane, or other organic solvents or mixtures thereof. There is thus obtained 11-hydroxy-7 α -methyl-19-norandrostenedione (XIV; identical to XI wherein $Z=\alpha$ or β -hydroxy).

The compound (XIV) so obtained is then converted to the corresponding 3-enamine (XVI) using the procedure described above for the preparation of the corresponding 11-desoxy 3-enamine (XII).

The 11-hydroxy-7 α -methyl-19-norandrostenedione 3-enamine (XVI) so obtained is alkylated using any of the alkylating agents and alkylating procedures described above for the alkylation of the corresponding 11-desoxy 3-enamine (XIII). There is thus obtained the corresponding 17-alkylated-11-hydroxy-7 α -methyl-19-nortestosterone 3-enamine (XVIII) which is generally not isolated as such from the reaction mixture after alkylation but is hydrolyzed in situ to the corresponding 11-hydroxy-7 α -methyl-17-alkylated-19-nortestosterone (XIX), for example, by treatment with an aqueous solution of a base such as sodium hydroxide or potassium hydroxide.

The compounds having the formula (VIII), which are employed as starting materials in the processes of Reaction Scheme B, can be prepared as follows:

The preparation of 6-dehydro-19-nortestosterone acetate (VIII; $R^{11}=H$, $Y=CH_3CO$) by reaction of 19-nortestosterone with acetic anhydride and acetyl chloride in pyridine solution, followed by bromination of the resulting 3,17 β -diacetoxy-19-nor- $\Delta^{3,5}$ -androstadiene and dehydrobromination of the 6-bromo-19-nortestosterone 17-acetate so formed, has been described in British Patent Specification 833,183. Replacing the acetic anhydride and acetyl chloride employed in the first step of the above process by the appropriate acid anhydride and acid chloride yields other 17-acylates having the formula (VIII; $R^{11}=H$, $Y=Ac$). The corresponding 17-hydroxy compounds (VIII; $R^{11}=H$, $Y=H$) can be prepared by deacylation of the 17-acylates using procedures well known in the art.

Replacing 19-nortestosterone by the appropriate 17-alkyl-19-nortestosterone and employing the appropriate acid anhydride and acid halide in the above-described process affords the requisite 17-alkyl-6-dehydro-19-nortestosterone 17-acylate (VIII; $R^{11}=alkyl$, $Y=acyl$). The corresponding free 17-hydroxy compounds (VIII; $R^{11}=alkyl$, $Y=H$) can be prepared by deacylation of the 17-acylates using procedures well known in the art, for example, using a base such as sodium hydroxide or potassium hydroxide in aqueous or aqueous alcoholic solution.

This invention also includes the compound 7 α -methyl-17 α -ethyltestosterone and the 17-acylates thereof. These compounds have androgenic and anabolic activity of improved therapeutic ratio and also possess antiestrogenic, gonadotropin-inhibiting activity, progestational, growth promoting, and central nervous system regulating activities which make them useful in the treatment of mammals in medical and veterinary practice.

The compound 7 α -methyl-17 α -ethyltestosterone can be prepared by reacting 6-dehydro-17 α -ethyltestosterone (U.S. Patent 2,739,974) with a methyl Grignard reagent in the presence of an agent such as a cuprous halide preferably cuprous chloride or cuprous bromide using the conditions hereinbefore described for the conversion of compound (VII) to compound (IX) in Reaction Scheme B.

Alternatively, 7 α -methyl-17 α -ethyltestosterone can be prepared from 7 α -methyltestosterone by oxidizing the latter compound to 7 α -methylandrostene-3,17-dione using procedures known in the art, for example, using chromic acid, sodium dichromate, potassium dichromate and like oxidizing agents. The 7 α -methylandrostene-3,17-dione is then converted to the corresponding 3-enamine using pyrrolidine and like secondary cyclic alkylene amines, according to the procedures described above for the preparation of the 3-enamines (XIII) and (XVI). The 3-enamine of 7 α -methylandrostene-3,17-dione is then reacted with an ethyl Grignard reagent such as ethyl magnesium bromide, in the presence of a solvent such as dimethylether, tetrahydrofuran or benzene. Preferably the ethyl Grignard reagent is employed in an excess of the order of 10 moles per

mole of the 3-enamine. The resulting 3-enamine of 7 α -methyl-17 α -ethyltestosterone is generally not isolated from the reaction mixture but is hydrolyzed in situ to the corresponding 7 α -methyl-17 α -ethyltestosterone by treatment with an aqueous solution of a base such as sodium hydroxide or potassium hydroxide, after first decomposing the reaction mixture with water or ammonium chloride.

In an alternative method of preparation the 3-enamine of 7 α -methyl-17 α -ethyltestosterone is reacted with an alkali metal derivative, for example, the sodium or potassium derivative of acetylene. The reaction is carried out preferably in the presence of an inert solvent such as dimethylformamide or dimethylsulphoxide. The 3-enamine of 7 α -methyl-17 α -ethyltestosterone so obtained is not generally isolated from the reaction mixture but is hydrolyzed in situ as described above to obtain 7 α -methyl-17 α -ethyltestosterone. The latter compound is then hydrogenated in the presence of a suitable hydrogenation catalyst such as palladium-on-charcoal to obtain the desired 7 α -methyl-17 α -ethyltestosterone.

The 17-acylates of 7 α -methyl-17 α -ethyltestosterone can be prepared from the latter compound using procedures known in the art, for example, by treatment with the appropriate acid anhydride or acid halide in the presence of a tertiary base such as pyridine.

The following examples are illustrative of the process and products of the present invention, but are not to be construed as limiting.

EXAMPLE 1.

1-dehydro-7 α ,17 α -dimethyltestosterone.

A mixture of 8.0 g. of 7 α ,17 α -dimethyltestosterone, 8.0 g. of mercury, 6.5 ml. of acetic acid, 5.0 g. of selenium dioxide and 300 ml. of t-butyl alcohol was stirred and refluxed under nitrogen for 4 hours. An additional 2.0 grams of selenium dioxide was added and after refluxing for a total of 7 hours the reaction mixture was concentrated to about 200 milliliters under a fast stream of nitrogen. After diluting with a mixture of methylene chloride and ether, the solution was washed three times with freshly prepared ammonium sulfide, twice with diluted ammonium hydroxide and twice with water. The washed solution was dried, filtered and concentrated to dryness. The gummy product was dissolved in methylene chloride and poured on a 200 g. Florisil, Registered Trade Mark, column packed wet with Skellysolve B. The column was washed with increasing amounts of acetone in Skellysolve B. Those fractions of eluted material which were identified as 1-dehydro-7 α ,17 α -dimethyltestosterone by paper chromatogram analysis were combined and recrystallized from a mixture of acetone and Skellysolve B. There was thus obtained 1-dehydro-7 α ,17 α -dimethyltestosterone in the form of a white crystalline solid having a melting point of 153 to 156 degrees centigrade; $[\alpha]_D - 6$ degrees (chloroform, $\lambda_{\text{max}}^{\text{alc.}}$, 243.5 m μ , $n_D^{20} = 1.5500$.

Anal. Calculated for C₂₇H₃₈O₂: C, 80.21; H, 9.62.
Found: C, 80.29; H, 9.76.

EXAMPLE 2.

1-dehydro-7 α ,17 α -dimethyl-11 β -hydroxytestosterone.

Following the procedure of Example 1, but substituting 7 α ,17 α -dimethyl-11 β -hydroxytestosterone for 7 α ,17 α -dimethyltestosterone, there is obtained 1-dehydro-7 α ,17 α -dimethyl-11 β -hydroxytestosterone.

EXAMPLE 3.

7,17-dimethyl-1,9(11)-bisdehydrotestosterone.

Following the procedure of Example 1, but substituting 7,17-dimethyl-9(11)-dehydrotestosterone for 7 α ,17 α -dimethyltestosterone, there is obtained 7,17-dimethyl-1,9(11)-bisdehydrotestosterone.

EXAMPLE 4.

1-dehydro-7-methyl-11 β -hydroxytestosterone.

Following the procedure of Example 1, but substituting 7-methyl-11 β -hydroxytestosterone for 7 α ,17 α -dimethyltestosterone, there is obtained 1-dehydro-7-methyl-11 β -hydroxytestosterone.

Similarly, 7-methyltestosterone, 7-methyl-11 α -hydroxytestosterone, 7,17-dimethyl-11 α -hydroxytestosterone, 7-methyl-11-ketotestosterone, 7-methyl-9(11)-dehydrotestosterone,

sterone and 7,17-dimethyl-11-ketotestosterone are converted to 1-dehydro-7-methyltestosterone, 1-dehydro-11 α -hydroxy-7-methyltestosterone, 1-dehydro-7,17-dimethyl-11 α -hydroxytestosterone, 1-dehydro-7-methyl-11-ketotestosterone, 7-methyl-1,9(11)-bisdehydrotestosterone, and 1-dehydro-7,17-dimethyl-11-ketotestosterone, respectively.

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EXAMPLE 5.

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1-dehydro-7-methyl-11 β -hydroxytestosterone 17-acetate.

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A solution of 1.0 gram of 1-dehydro-7-methyl-11 β -hydroxytestosterone, dissolved in six milliliters of dried and redistilled pyridine, was treated with six milliliters of acetic anhydride. After standing at room temperature for seventeen hours, it was poured into ice water. The mixture was filtered after two hours of standing and the precipitate was washed with water and dried in vacuo. Upon recrystallization from an acetone-hexane mixture substantially pure 1-dehydro-7-methyl-11 β -hydroxytestosterone 17-acetate was obtained.

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In the same manner as given in Example 5, by the reaction of 1-dehydro-7-methyl-11 β -hydroxytestosterone with propionic anhydride, 1-dehydro-7-methyl-11 β -hydroxytestosterone 17-propionate was obtained.

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EXAMPLE 6.

1-dehydro-7-methyl-11 β -hydroxytestosterone 17-benzoate.

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Three-tenths gram (0.3 gram) of 1-dehydro-7-methyl-11 β -hydroxytestosterone, suspended in twelve milliliters of dry benzene, was treated with 0.3 milliliter of distilled benzoyl chloride and 0.3 milliliter of dry pyridine. The mixture was stirred for seventeen hours at room temperature. After refrigeration, the product was collected on a filter, washed with benzene and ether, and dried. Recrystallization from ethyl acetate gave substantially pure 1-dehydro-7-methyl-11 β -hydroxytestosterone 17-benzoate.

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In the same manner as given in Example 3 the 17 β -cyclopentylpropionate, butyrate, isobutyrate, valerate, isovalerate, hexanoate, heptanoate, octanoate, phenylacetate, p-hexyloxyphenylpropionate, and other like 17-esters of 1-dehydro-7-methyl-11 β -hydroxytestosterone are prepared by the reaction of 1-dehydro-7-methyl-11 β -hydroxytestosterone with the selected acid anhydride or halide. Treatment of 1-dehydro-7-methyl-11 β -hydroxytestosterone with formic acid produces 1-dehydro-7-methyl-11 β -hydroxytestosterone 17-formate.

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Similarly, following the procedure of Examples 5 and 6 and the paragraphs following 1-dehydro-7-methyltestosterone, and 1-dehydro-7-methyl-11-ketotestosterone are converted to their 17-acetate, 17-propionate, 17-benzoate and the other esters named therein.

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Substituting 1-dehydro-7-methyl-11 α -hydroxytestosterone as the starting steroid in the reactions described in Example 3 and the paragraph following is productive of the corresponding 11 α ,17-diester of 1-dehydro-7-methyl-11 α -hydroxytestosterone.

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EXAMPLE 7.

1-dehydro-7-methyl-11-ketotestosterone 17-benzoate.

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A solution of 1.5 grams of 1-dehydro-7-methyl-11 β -hydroxytestosterone 17-benzoate in eighty milliliters of acetic acid was treated with a solution of 0.74 gram of chromic acid anhydride in four milliliters of water and eighty milliliters of acetic acid and allowed to stand at room temperature for five hours. The excess chromic acid was destroyed by the addition of ten milliliters of methanol and the solution was concentrated in vacuo on a water bath. The residue, after trituration with water, was extracted with ether and the ether solution washed with dilute sodium hydroxide solution and water, and then dried over anhydrous sodium sulphate. Upon evaporation of the ether there was obtained 1-dehydro-7-methyl-11-ketotestosterone 17-benzoate.

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EXAMPLE 8.

1-dehydro-7-methyl-11-ketotestosterone 17-acetate.

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A solution of 1-dehydro-7-methyl-11 β -hydroxytestosterone 17-acetate in acetic acid was agitated for twelve hours with an aqueous solution of chromic acid anhydride. The steroid product was extracted thoroughly with benzene which was washed with a sodium bicarbonate solution and then water, dried over anhydrous sodium sulphate, and evaporated to give 1-dehydro-7-methyl-11-ketotestosterone 17-acetate.

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In the same manner as given in Example 7 and 8, 1-dehydro-7-methyl-11-ketotestosterone 17-formate, 17-butyrate, 17-isobutyrate, 17-valerate, 17-isovalerate, 17-hexanoate, 17-heptanoate, 17-octanoate, 17-benzoate, 17-phenylacetate, 17(β -cyclopentyl)-propionate, 17-p-butyloxyphenylpropionate, and like 17-esters of 1-dehydro-

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7-methyl-11-ketotestosterone are prepared by reaction of the corresponding 7-methyl-11 β -hydroxytestosterone 17-ester with chromic anhydride in acetic acid or with an acidified dichromate solution.

Following the procedure of Example 7, 1-dehydro-7,17-dimethyl-11 β -hydroxytestosterone is converted to 1-dehydro-7,17-dimethyl-11-ketotestosterone.

EXAMPLE 9.

1-dehydro-7-methyl-11-ketotestosterone.

A solution of 1.0 gram of 1-dehydro-7-methyl-11-ketotestosterone 17-propionate in fifty milliliters of 1 normal methanolic potassium hydroxide solution containing three milliliters of water was refluxed for a period of thirty minutes. The solution was poured onto ice and the mixture neutralized with dilute sulfuric acid. After standing, the resulting precipitate was recovered, washed with water and dried. The aqueous filtrate was extracted with methylene chloride to recover an additional amount of material. Substantially pure 1-dehydro-7-methyl-11-ketotestosterone is obtained when this residue is recrystallized from methylene chloride.

EXAMPLE 10.

1-dehydro-7-methyl-9(11)-dehydrotestosterone.

A two-phase mixture of 2.5 grams of 1-dehydro-7-methyl-11 β -hydroxytestosterone, 250 milliliters of benzene, 200 milliliters of ether, 100 milliliters of concentrated hydrochloric acid, and 100 milliliters of water was heated under reflux for eighteen hours with vigorous stirring. After cooling, the two layers were separated and the aqueous layer extracted three times with 75-milliliter portions of ether. The ether extracts were combined with the benzene-ether layer, and then washed with dilute aqueous potassium carbonate solution and with water. The washed solution was dried over anhydrous sodium sulfate and, after removal of the drying agent, the solvent was evaporated. The residue was recrystallized from a mixture of methylene chloride and hexane hydrocarbons (Skellysolve B) to provide 1-dehydro-7-methyl-9-(11)-dehydrotestosterone.

EXAMPLE 11.

1-dehydro-7-methyl-9(11)-dehydrotestosterone 17-propionate.

A solution of 250 milligrams of 1-dehydro-7-methyl-9(11)-dehydrotestosterone in thirty milliliters of benzene was prepared, and eighteen milliliters of benzene was distilled to dry the solution. After cooling, the dried solution was treated with two milliliters of dry pyridine and two milliliters of propionic anhydride and maintained at a temperature of about 26 degrees centigrade for 22 hours. The mixture was then treated with 25 milliliters of water and extracted with ether. The ether extract was washed with dilute aqueous hydrochloric acid and then with dilute aqueous sodium hydroxide solution, followed by water. The solution was dried over anhydrous sodium sulphate, and, after removing the drying agent, the solvent was evaporated in vacuo. The residue was crystallized from absolute methanol to yield substantially pure 1-dehydro-7-methyl-9(11)-dehydrotestosterone 17-propionate.

In the same manner, but employing benzoyl chloride, 1-dehydro-7-methyl-9(11)-dehydrotestosterone 17-benzoate is prepared.

EXAMPLE 12.

1-dehydro-7-methyl-9(11)-dehydrotestosterone 17-(β -cyclopentylpropionate).

A solution of 250 milligrams of 1-dehydro-7-methyl-9(11)-dehydrotestosterone in 25 milliliters of benzene was prepared and dried by distilling twelve milliliters of benzene from the solution. After cooling, the solution was treated with 0.25 milliliter of dry pyridine and 0.25 milliliter of β -cyclopentylpropionyl chloride and was maintained at about 26 degrees centigrade for five hours, during which time pyridine hydrochloride separated. The resulting mixture was treated with twenty milliliters of water and then extracted with ether. After washing the ether extract with dilute aqueous hydrochloric acid, dilute aqueous sodium hydroxide, and water, it was dried over anhydrous sodium sulphate. After removal of the drying agent, the solvent was evaporated to give a residue of 1-dehydro-7-methyl-9(11)-dehydrotestosterone 17-(β -cyclopentylpropionate).

In the same manner reacting 7-methyl-1,9(11)-dehydrotestosterone with the appropriate acylating agent provides other representative 17-cycloalkylalkanoates of 7-methyl-1,9(11)-dehydrotestosterone, including the 17-cyclopentylformate, cyclohexylformate, cyclopentylacetate, cyclobutylformate,

α -cyclopentylpropionate, cyclohexylacetate, cyclopropylformate, cycloheptylformate, β -(methylcyclopentyl)-acetate, β -cyclobutylpropionate, and other 17-cycloalkyl-alkanoates.

- 5 In the same manner as shown in Examples 11 and 12 other acylates of 7-methyl-1,9(11)-bisdehydrotestosterone are prepared by reacting 7-methyl-1,9(11)-bisdehydrotestosterone, preferably in pyridine solution, with the acyl halide or the anhydride of a hydrocarbon carboxylic acid preferably containing from one to twelve carbon atoms, inclusive. Other representative esters of 7-methyl-1,9(11)-bisdehydrotestosterone thus-prepared include the acetate, butyrate isobutyrate, valerate, isovalerate, hexanoate, heptanoate, octanoate, phenylacetate, phenylpropionate, p-hexyloxyphenylpropionate, and trimethylacetate. 10

EXAMPLE 13.

1-dehydro-7-methyl-9 α -bromo-11 β -hydroxytestosterone 17-propionate.

- 15 Two grams of 1-dehydro-7-methyl-9(11)-dehydrotestosterone 17-propionate, dissolved in 100 milliliters of acetone, were cooled to fifteen degrees centigrade and the solution was thereupon treated with two grams of N-bromoacetamide, dissolved in fifty milliliters of water. Maintaining the bath temperature at twelve degrees centigrade, a solution of ten milliliters of 0.8N perchloric acid was added. Five minutes later another ten milliliters of perchloric acid was added and after ten more minutes a final 20 twenty milliliters of the same 0.8N perchloric acid was added. At the end of twenty minutes total reaction time, a saturated solution of sodium sulphite was added slowly with mixing. The mixture was thereupon diluted with 200 milliliters of water and the product, thus separated, was recovered by filtration, washed well with water and dried over anhydrous sodium sulphate, and the solvent separated by distillation, leaving a residue of 7-methyl-9 α -bromo-11 β -hydroxytestosterone 17-propionate. 25

- In the same manner as given in Example 13, 7-methyl-1,9(11)-bisdehydrotestosterone 17-benzoate, 7-methyl-1,9(11)-bisdehydrotestosterone 17-acetate, 7-methyl-1,9(11)-bisdehydrotestosterone 17-butyrate, 7-methyl-1,9(11)-bisdehydrotestosterone 17-isobutyrate, 7-methyl-1,9(11)-bisdehydrotestosterone 17-valerate, 7-methyl-1,9(11)-bisdehydrotestosterone 17-hexanoate, 7-methyl-1,9(11)-bisdehydrotestosterone 17-(β -cyclopentylpropionate) and 7-methyl-1,9(11)-bisdehydrotestosterone 17-phenylacetate gave the corresponding 1-dehydro-7-methyl-9 α -bromo-11 β -hydroxytestosterone 17-acylates by reaction with N-bromoacetamide in acetone solution in the presence of aqueous perchloric acid. 30

EXAMPLE 14.

1-dehydro-7-methyl-9 α -chloro-11 β -hydroxytestosterone 17-propionate.

- 35 One gram of 7-methyl-1,9(11)-bisdehydrotestosterone 17-propionate, dissolved in fifty milliliters of tertiary butyl alcohol, was treated at room temperature, about twenty to 25 degrees centigrade, with one gram of N-chlorosuccinimide, dissolved in tertiary butyl alcohol. To this solution was added fifty milliliters of 0.1N sulphuric acid. The mixture was stirred for a period of thirty minutes at room temperature and thereupon diluted with 300 milliliters of water and extracted with three fifty-milliliter portions of methylene chloride. The methylene chloride extracts were dried over anhydrous sodium sulphate and evaporated to give a residue which was recrystallized twice from methanol to give 1-dehydro-7-methyl-9 α -chloro-11 β -hydroxytestosterone 17-propionate. 40 45

EXAMPLE 15.

1-dehydro-7,17-dimethyl-9 α -bromo-11 β -hydroxytestosterone.

- 50 One gram of 1-dehydro-7,17-dimethyl-9(11)-dehydrotestosterone, dissolved in dioxane (fifty milliliters), was reacted at about 24 degrees centigrade with one gram of N-bromo-succinimide, dissolved in fifty milliliters of dioxane. To this solution was added fifty milliliters of 0.1N sulphuric acid and the mixture was agitated at room temperature for a period of one hour. Thereafter, 300 milliliters of water was added and the reaction mixture was extracted with three fifty-milliliter portions of methylene chloride. The methylene chloride solution was washed with sodium thiosulphate solution and then with water and then dried over anhydrous sodium sulphate. Evaporation of the dried methylene chloride solution gave a residue which, after recrystallization from methanol, gave 1-dehydro-7,17-dimethyl-9 α -bromo-11 β -hydroxytestosterone. 55

- In the same manner as shown in Examples 13 to 15, inclusive, reacting 7-methyl-1,9(11)-bisdehydrotestosterone 17-acylate in tertiary butyl alcohol, dioxane, acetone, or the like, with a hypohalous acid, preferably produced by reaction of a strong acid such as perchloric, sulphuric, trichloroacetic acid and an N-haloamide or an N-haloimide 60

especially N-haloacetamide or N-halosuccinimide produces the corresponding 1-dehydro-7-methyl-9 α -halo-11 β -hydroxytestosterone 17-acylate. Other such 1-dehydro-7-methyl-9 α -halo-11 β -hydroxytestosterone 17-acylates thus produced include the 17-acetate, propionate, butyrate, valerate, isovalerate, β -cyclopentylpropionate, benzoate, phenylacetate, toluate, β -cyclopentylpropionate of 1-dehydro-7-methyl-9 α -iodo-11 β -hydroxytestosterone, and 1-dehydro-7-methyl-9 α -chloro-11 β -hydroxytestosterone.

If 1-dehydro-7-methyl-9 α -halo-11 β -hydroxytestosterone 17-acylates are desired wherein the acyl radical is of an unsaturated acid such as acrylic, crotonic, cinnamic, fumaric, or maleic acid or the like, the selected 1-dehydro-7-methyl-9 α -halo-11 β -hydroxytestosterone is reacted with the acid halide of such unsaturated acid to give the corresponding 1-dehydro-7-methyl-9 α -halo-11 β -hydroxytestosterone 17-acylate.

EXAMPLE 16.

1-dehydro-7-methyl-9 β ,11 β -epoxytestosterone 17-propionate.

A solution of 1.36 grams of 1-dehydro-7-methyl-9 α -bromo-11 β -hydroxytestosterone propionate, dissolved in fifty milliliters of methanol was titrated with 0.1N aqueous sodium hydroxide until the solution remained basic to phenolphthalein upon standing for a period of thirty seconds. About 32 milliliters of base, equal to one equivalent, was required. Thereafter 300 milliliters of water was slowly added with stirring. The mixture was cooled and thereafter filtered and the precipitate thus obtained washed with water and dried over anhydrous sodium sulphate to give crude 1-dehydro-7-methyl-9 β ,11 β -epoxytestosterone 17-propionate which was recrystallized from dilute methanol to give a substantially pure sample.

In the same manner given in Example 16, 1-dehydro-7-methyl-9 α -bromo-11 β -hydroxytestosterone was titrated with aqueous sodium hydroxide solution until the reaction mixture became basic to phenolphthalein for about one-half minute. The solution was then diluted with water and filtered to give a precipitate of 1-dehydro-7-methyl-9 β ,11 β -epoxytestosterone.

EXAMPLE 17.

1-dehydro-7,17-dimethyl-9 β ,11 β -epoxytestosterone.

A mixture of 1-dehydro-7,17-dimethyl-9 α -bromo-11 β -hydroxytestosterone, potassium acetate and tertiary butyl alcohol was heated on a water bath for a period of one hour. The mixture was thereupon poured into ice water and the resulting precipitate collected on filter and recrystallized to give substantially pure 7,17-dimethyl-9 β ,11 β -epoxytestosterone.

In the same manner as shown in Example 17, other 1-dehydro-7-methyl-9 β ,11 β -epoxytestosterone 17-acylates are produced by reacting the 1-dehydro-7-methyl-9 α -halo-11 β -hydroxytestosterone 17-acylates described in Example 15 with a mild base. Representative 17-acylates thus produced include the 17-acetate, butyrate, isobutyrate, valerate, isovalerate, hexanoate, heptanoate, octanoate, toluate, trimethylacetate, acrylate, crotonate, and β -cyclopentylpropionate of 1-dehydro-7-methyl-9 β ,11 β -epoxytestosterone.

EXAMPLE 18.

1-dehydro-7-methyl-9 α -fluoro-11 β -hydroxytestosterone 17-propionate.

A chilled solution of 1.13 grams of 1-dehydro-7-methyl-9 β ,11 β -epoxytestosterone 17-propionate in twenty milliliters of alcohol-free chloroform was added to a chilled solution of alcohol-free chloroform into which hydrogen fluoride gas had been introduced for a period of three minutes. The mixture, contained in a polyethylene bottle, was maintained at minus fifteen degrees centigrade for a period of four hours and thereafter was poured into an excess of a saturated sodium bicarbonate solution. The aqueous layer was separated from the chloroform layer and extracted three times with chloroform. The combined chloroform layer and extracts were washed with water, dried over anhydrous sodium sulphate and the solvent evaporated to give a residue of 7-methyl-9 α -fluoro-11 β -hydroxytestosterone 17-propionate which was purified by chromatography over 100 grams of anhydrous magnesium silicate (Florisil) developed with from 20 to 1 to 9 to 1 mixture of hexane hydrocarbons (Skellysolve B) and acetone. The solvent was evaporated from the eluate fractions leaving 1-dehydro-7-methyl-9 α -fluoro-11 β -hydroxytestosterone 17-propionate as the main solid fraction.

EXAMPLE 19.

1-dehydro-7,17-dimethyl-9 α -fluoro-11 β -hydroxytestosterone.

In the same manner as shown in Example 18, 1-dehydro-7,17-dimethyl-9 β ,11 β -epoxytestosterone was treated with hydrogen fluoride gas dissolved in alcohol-free

chloroform to give 1-dehydro-7,17-dimethyl-9 α -fluoro-11 β -hydroxytestosterone, respectively.

In the same manner as given in Example 18, reacting any of the 9 β ,11 β -epoxides described in Example 17 and the paragraphs following, in methylene chloride with hydrogen fluoride or with aqueous hydrofluoric acid in the presence of perchloric acid is productive of the corresponding 1-dehydro-7-methyl-9 α -fluoro-11 β -hydroxytestosterone acylate, e.g., 1-dehydro-7-methyl-9 α -fluoro-11 β -hydroxytestosterone 17-acetate and 17-propionate, and other 1-dehydro-7-methyl-9 α -fluoro-11 β -hydroxytestosterone 17-acylates including the 17-butyrate, isobutyrate, valerate, isovalerate, hexanoate, heptanoate, octanoate, phenylpropionate, toluate, cinnamate, p-butyloxyphenylpropionate, and trimethylacetate.

EXAMPLE 20.

1-dehydro-7-methyl-9 α -fluoro-11-ketotestosterone 17-propionate.

A solution of 0.779 gram of 1-dehydro-7-methyl-9 α -fluoro-11 β -hydroxytestosterone 17-propionate in forty milliliters of glacial acetic acid was treated with a solution of 0.37 gram of chromium trioxide, dissolved in two milliliters of water and forty milliliters of glacial acetic acid. The reaction mixture was allowed to stand at room temperature for a period of five hours. Thereafter, ten milliliters of methanol was added, then 200 milliliters of water, and the mixture was extracted with ether, the ether fraction washed with sodium bicarbonate solution and water, evaporated, the residue recrystallized from methylene chloride-hexane hydrocarbons solution and finally from dilute acetone to give 1-dehydro-7-methyl-9 α -fluoro-11-ketotestosterone 17-propionate.

Following the procedure of Example 16, 1-dehydro-7-methyl-9 α -fluoro-11 β -hydroxytestosterone 17-propionate was converted to 1-dehydro-7-methyl-9 α -fluoro-11-ketotestosterone 17-propionate, and 1-dehydro-7,17-dimethyl-9 α -fluoro-11 β -hydroxytestosterone was converted to 1-dehydro-7,17-dimethyl-9 α -fluoro-11 β -hydroxytestosterone.

In the same manner as shown in Example 16, 1-dehydro-7-methyl-9 α -chloro-11 β -hydroxytestosterone 17-propionate was oxidized with chromium trioxide in glacial acetic acid to give 1-dehydro-7-methyl-9 α -chloro-11-ketotestosterone 17-propionate. 1-dehydro-7-methyl-9 α -iodo-11 β -hydroxytestosterone 17-propionate gave, 1-dehydro-7-methyl-9 α -iodo-11-ketotestosterone 17-propionate, 1-dehydro-7-methyl-9 α -fluoro-11 β -hydroxytestosterone 17-benzoate gave, 1-dehydro-7-methyl-9 α -fluoro-11-ketotestosterone 17-benzoate and 1-dehydro-7-methyl-9 α -fluoro-11 β -hydroxytestosterone 17-phenylacetate gave 1-dehydro-7-methyl-9 α -fluoro-11-ketotestosterone 17-phenylacetate.

In the same manner given in Example 16, oxidizing the corresponding 9 α -halo-11 β -hydroxy compound in glacial acetic acid solution with chromic trioxide produced the following compounds: 1-dehydro-7-methyl-9 α -fluoro-11-ketotestosterone 17-acetate; 1-dehydro-7-methyl-9 α -fluoro-11-ketotestosterone 17-(β -cyclopentylpropionate); 1-dehydro-7-methyl-9 α -fluoro-11-ketotestosterone 17-butyrate, isobutyrate, valerate, isovalerate, hexanoate, heptanoate, octanoate, phenylpropionate, toluate, and trimethylacetate.

1-Dehydro-7-methyl-9 α -fluoro-11-ketotestosterone 17-acylates may also be obtained by acylation of the free 1-dehydro-7-methyl-9 α -fluoro-11-ketotestosterone with acyl halides or acid anhydride, preferably of hydrocarbon carboxylic acids containing from one to twelve carbon atoms, inclusive, and in the preferred embodiment in pyridine solution. This method is preferred for obtaining 1-dehydro-7-methyl-9 α -fluoro-11-ketotestosterone 17-acylates wherein the 17-acyloxy group is easily attacked by chromic acid such as in cases wherein an unsaturated acid, e.g., acrylic, crotonic, or similar acids are desired.

In the same manner as shown for the production of 1-dehydro-7-methyl-9 α -fluoro-11-ketotestosterone 17-acylates other 1-dehydro-7-methyl-9 α -halo-11-ketotestosterone 17-acylates are produced by either oxidizing the corresponding 1-dehydro-7-methyl-9 α -halo-11 β -hydroxytestosterone 17-acylate or by esterifying the 1-dehydro-7-methyl-9 α -halo-11-ketotestosterone wherein the halogen atom is chlorine, bromine, or iodine. In this manner, the acetates, butyrates, isobutyrate, valerates, isovalerates, hexanoates, heptanoates, octanoates, benzoates, phenylacetates, toluates, cinnamates, and other esters of 1-dehydro-7-methyl-9 α -chloro, 7-methyl-9 α -bromo and 1-dehydro-7-methyl-9 α -iodo-11-ketotestosterone, are produced.

EXAMPLE 21.

1-dehydro-7-methyl-9 α -fluoro-11-ketotestosterone.

A solution of 0.5 gram of 1-dehydro-7-methyl-9 α -fluoro-11-ketotestosterone 17-propionate, eighty milligrams of potassium hydroxide in ten milliliters of ethanol and one milliliter of water was heated on the water bath for a period of one hour. Thereafter the mixture was poured in fifty milliliters of water and neutralized with dilute hydrochloric acid. The aqueous reaction mixture was thereupon extracted with three fifty-milliliter portions of methylene chloride, the methylene chloride solution was washed repeatedly with water, dried over anhydrous sodium sulphate and evaporated and the residues thus obtained recrystallized from acetone-Skellysolve B hexanes to give 1-dehydro-7-methyl-9 α -fluoro-11-ketotestosterone.

EXAMPLE 22.

1-dehydro-7-methyl-9 α -fluoro-11 β -hydroxytestosterone.

A solution of one gram of 1-dehydro-7-methyl-9 α -fluoro-11 β -hydroxytestosterone 17-acetate in methanol was freed of oxygen gas by bubbling nitrogen therethrough. A solution of one gram of potassium bicarbonate in ten milliliters of water was similarly freed of oxygen. The two solutions were mixed at a temperature of between eighteen and twenty degrees centigrade and in a nitrogen atmosphere. The mixture was stirred at room temperature for twenty hours while protecting it from atmospheric oxygen with nitrogen. At the end of twenty hours the solution was neutralized by the addition of ice water containing acetic acid. The neutralized solution was concentrated to about sixty milliliters by distillation at room temperature at reduced pressure and then chilled in a refrigerator for about sixteen hours. The thus-precipitated 1-dehydro-7-methyl-9 α -fluoro-11 β -hydroxytestosterone was filtered, washed with water, dried and recrystallized to give 1-dehydro-7-methyl-9 α -fluoro-11 β -hydroxytestosterone.

EXAMPLE 23.

7 α -methyl-19-nortestosterone acetate.

To 30 ml. of tetrahydrofuran (prepared by percolating commercial grade tetrahydrofuran through a column of neutral alumina and discarding the first 15 ml. of percolate) cooled in an ice-bath was added, with stirring under an atmosphere of nitrogen, 25 ml. of a 3M solution of methyl-magnesium bromide in ether followed of 0.4 g. of cuprous bromide. To the stirred mixture so obtained was added a slurry of a small amount of cuprous bromide in a solution of 3 g. of 6-dehydro-19-nortestosterone 17-acetate in 50 ml. of tetrahydrofuran (previously treated as described above). The resulting mixture was stirred with cooling for a further ten minutes and was then poured into a mixture of ice-diluted hydrochloric acid saturated with sodium chloride-ether which was purged with nitrogen. The ether phase was separated and washed successively with brine, diluted sodium hydroxide - brine, and finally with brine. The ether extracts were combined and dried over anhydrous magnesium sulphate. The dried solution was filtered and the filtrate was evaporated to dryness. The residue was dissolved in 5 ml. of pyridine and 5 ml. of acetic anhydride. After standing at room temperature for 18 hrs. ice and water were added and the product was extracted with ether. The extract was washed with dilute acid, dilute sodium hydroxide and water, dried and the solvent removed. The residue was dissolved in methylene chloride and chromatographed on a column of magnesium silicate (Florisil). The column was eluted with Skellysolve B hexanes containing increasing proportions of acetone and those fractions, which were found by infrared analysis to contain the desired 7 α -methyl-19-nortestosterone 17-acetate, were combined and evaporated to dryness. The oily residue was dissolved in acetone and chromatographed on a 30 g. 2:1 Celite:Darco column packed wet with acetone. The column was eluted with acetone and the first 750 ml. of eluate was evaporated to dryness. The residue was recrystallized from aqueous methanol. There was thus obtained 1 g. of 7 α -methyl-19-nortestosterone 17-acetate in the form of a crystalline solid having a melting point of 111 to 114° C.; $[\alpha]_D + 48^\circ$ (chloroform). The ultraviolet absorption spectrum of this compound (in solution in ethanol) exhibited a maximum at 240 millimicrons ($\epsilon = 17,350$).

Anal: Calcd. for C₂₁H₃₀O₂: C, 76.32; H, 9.15
 Found: C, 76.28; H, 9.44.

EXAMPLE 24.

7 α -methyl-19-nortestosterone.

A solution of 3 g. of 7 α -methyl-19-nortestosterone 17-acetate in 40 ml. of a 5 percent solution of potassium carbonate in 80 percent aqueous methanol was heated under reflux in an atmosphere of nitrogen for 2 hours. The reaction mixture was extracted with ether and the ethereal extract was washed with water and dried over anhydrous magnesium sulphate. The dried ether solution was filtered and the filtrate was evaporated to dryness. The residue was triturated with ether and the solid which separated was isolated by filtration. There was thus obtained 7 α -methyl-19-nortestosterone in the form of a crystalline solid having a melting point of 140 to 145.5° C. An analytical sample having a melting point of 145 to 146° C. and $[\alpha]_D^{+55}$ (chloroform) was obtained by recrystallization from a mixture of acetone and Skellysolve B (a mixture of hexanes). The ultraviolet absorption spectrum of this compound (in solution in ethanol) exhibited a maximum at 241 millimicrons ($\epsilon = 17,150$).

Anal.: Calcd. for $C_{19}H_{26}O_2$: C, 79.12; H, 9.78
Found: C, 79.13; H, 10.19.

EXAMPLE 25.

7 α -methyl-19-norandrostene-3,17-dione.

To a slurry of 1.4 g. of chromium trioxide in 15 ml. of pyridine was added with stirring and cooling, a solution of 1.4 g. of 7 α -methyl-19-nortestosterone in 15 ml. of pyridine. After the addition was complete, the reaction mixture was stirred at room temperature (approximately 20° C.) for 20 hours and was then diluted with a mixture of equal parts of benzene and ether. The resulting mixture was filtered through a bed of diatomaceous earth (Celite). The filter bed was washed well with a mixture of equal parts of ether and benzene, then with water and finally with the mixed solvent. The filtrate and the organic layer of the washings were combined and washed several times with water. Each aqueous washing was back-extracted with a mixture of equal parts of ether and benzene. The combined organic layers were then dried and evaporated to dryness. The residue was triturated with ether and the solid material was isolated by filtration. There was thus obtained 1.4 g. of 7 α -methyl-19-norandrostene-3,17-dione in the form of a crystalline solid having a melting point of 195 to 198° C. An analytical sample having a melting point of 201 to 204° C. was obtained by recrystallization from acetone. The ultraviolet absorption spectrum of this compound (in solution in ethanol) exhibited a maximum of 239.5 millimicrons ($\epsilon = 17,000$).

Anal.: Calcd. for $C_{19}H_{26}O_2$: C, 79.69; H, 9.15
Found: C, 79.66; H, 8.87.

EXAMPLE 26.

7 α -methyl-19-norandrostene-3,17-dione 3-pyrrolidinyl enamine.

To a solution of 10 mg. of 7 α -methyl-19-norandrostene-3,17-dione in a little boiling methanol was added 1 drop of pyrrolidine. The resulting solution was concentrated by evaporation and allowed to cool. The crystalline solid which separated was isolated by filtration, washed with a small quantity of methanol and dried. There was thus obtained 7 α -methyl-19-norandrostene-3,17-dione 3-pyrrolidinyl enamine in the form of a crystalline solid having a melting point of 151 to 160° C. The ultraviolet absorption spectrum of the compound (in solution in ether) exhibited a maximum at 282 millimicrons ($\epsilon = 23,450$). The infrared absorption spectrum of the compound (mineral oil mull) exhibited maxima at 1735, 1635, 1600, 1200, 1180, 1155 and 1035 reciprocal centimeters.

EXAMPLE 27.

7 α -methyl-17 α -ethinyl-19-nortestosterone.

A volume of 1 ml. of a 20 percent by weight suspension of sodium acetylide in xylene was centrifuged and the solid which separated was taken up in 6 ml. of redistilled dimethylsulfoxide. To the resulting mixture was added the 3-pyrrolidyl enamine from 0.5 g. of 7 α -methyl-19-norandrostene-3,17-dione prepared as described in Example 30. The mixture so obtained was maintained under an atmosphere of nitrogen for five hours at the end of which time the excess sodium acetylide was destroyed by dropwise addition of water. About 2 ml. of water and 5 ml. of methanol was added to obtain a clear solution which was then heated on a steam bath for 1 hour. The mixture so obtained was extracted with ether and ethereal extract was washed successively with

dilute hydrochloric acid, dilute sodium carbonate and water before being dried over anhydrous magnesium sulphate. The dried solution was filtered and the filtrate was evaporated to dryness. The residue was triturated with a mixture of ether and Skellysolve B and recrystallized twice from a mixture of acetone and Skellysolve B. There was thus obtained 0.161 g. of 7 α -methyl-17 α -ethynyl-19-nortestosterone in the form of a crystalline solid having a melting point of 197 to 199.5° C. The ultraviolet spectrum of the compound (in solution in ethanol) exhibited a maximum at 240.5 millimicrons. The infrared absorption spectrum of the compound (mineral oil mull) exhibited maxima at 3390, 3240, 2100, 1663 and 1623 reciprocal centimeters.

Anal.: Calcd. for C₂₁H₂₈O₂: C, 80.72; H, 9.03
Found: C, 80.44; H, 9.05.

EXAMPLE 28.

17 α -ethyl-7 α -methyl-19-nortestosterone.

A suspension of 30 mg. of 1 percent palladium-on-charcoal catalyst in 20 milliliters of dioxane (purified as described by Fieser, Methods of Organic Chemistry, 2nd Edition, p 368) was saturated with hydrogen at atmospheric pressure. To the suspension was added 100 mg. of 7 α -methyl-17 α -ethynyl-19-nortestosterone and the mixture was hydrogenated at atmospheric pressure until 2 equivalents of hydrogen had been consumed. The reaction mixture was filtered through a bed of diatomaceous earth (Celite—Registered Trade Mark) and the filtrate was evaporated to dryness. The residue was combined with that obtained from a similar run employing 50 mg. of starting material. The combined residues were dissolved in methylene chloride and chromatographed on a column of 50 grams of magnesium silicate (Florisil—Registered Trade Mark) which had been packed wet with Skellysolve B. The column was eluted with Skellysolve B. The column was eluted with Skellysolve B containing increasing proportions of acetone and those fractions, which, on the basis of infrared analysis, contained the desired 17 α -ethyl-7 α -methyl-19-nortestosterone, were combined and evaporated to dryness. The residue was recrystallized twice from a mixture of Skellysolve B and ether. There was thus obtained 17 α -ethyl-7 α -methyl-19-nortestosterone in the form of a crystalline solid having a melting point of 138 to 139° C. The ultraviolet spectrum of the compound (in solution in ethanol) exhibited a maximum at 241 millimicrons (ϵ = 17,000).

Anal.: Calcd. for C₂₁H₃₂O₂: C, 79.69; H, 10.19
Found: C, 79.43; H, 10.23.

EXAMPLE 29.

7 α ,17 α -dimethyl-19-nortestosterone.

A solution of 2.75 g. of 7 α -methyl-19-norandrostene-3,17-dione 3-pyrrolidyl enamine in 70 ml. of tetrahydrofuran is added over a short period with stirring under an atmosphere of nitrogen to 25 ml. of a 3M solution of methylmagnesium bromide in diethyl ether. The resulting mixture is distilled until the vapor temperature reaches 55° C. and the residue is then heated under reflux for approximately 4 hours. To the mixture so obtained is added carefully with stirring an iced ammonium chloride solution followed by 130 ml. of methanol and 25 ml. of 5% aqueous sodium hydroxide. The mixture is stirred at 40° C. under nitrogen for several hours and is concentrated to about one third volume under reduced pressure. The resulting mixture is diluted with water and extracted with ether. The ether extract is washed successively with water, dilute hydrochloric acid, dilute aqueous sodium carbonate, and water before being dried over anhydrous sodium sulphate and filtered. The filtrate is evaporated to dryness and the residue is dissolved in methylene chloride and chromatographed over 100 grams of magnesium silicate (Florisil). The column is eluted with Skellysolve B containing increasing proportions of acetone and those fractions of the eluate which on infrared absorption analysis show no C—17 carbonyl absorption are combined and evaporated to dryness. The residue is recrystallized from a mixture of acetone and Skellysolve B. There is thus obtained 7 α ,17 α -dimethyl-19-nortestosterone in the form of a crystalline solid.

Using the above procedure but replacing methylmagnesium bromide by propylmagnesium bromide, isopropylmagnesium bromide, butylmagnesium bromide, allylmagnesium bromide, and 2-butenylmagnesium bromide, there are obtained 7 α -methyl-

ture for 5 hr. The excess chromic acid is destroyed by the addition of 10 ml. of methanol and the resulting solution is concentrated in vacuo with heating on a water-bath. The residue is triturated with water and then extracted with ether. The ether solution is washed with dilute sodium hydroxide solution and water before being dried over anhydrous sodium sulphate. The dried ether solution is evaporated to dryness and the residue is recrystallized from aqueous acetone. There is thus obtained 7 α ,17 α -dimethyl-11-keto-19-nortestosterone in the form of a crystalline solid.

The above compound is also obtained by employing 7 α ,17 α -dimethyl-11 β -hydroxy-19-nortestosterone as starting material in the above procedure.

Similarly, using the above procedure, but replacing 7 α ,17 α -dimethyl-11 α -hydroxy-19-nortestosterone by 17 α -ethyl-7 α -methyl-11 α -hydroxy-19-nortestosterone, 17 α -ethinyl-7 α -methyl-11 α -hydroxy-19-nortestosterone, 7 α -methyl-17 α -propyl-11 α -hydroxy-19-nortestosterone, 7 α -methyl-17 α -butyl-11 α -hydroxy-19-nortestosterone, 7 α -methyl-17 α -allyl-11 α -hydroxy-19-nortestosterone, of the corresponding 11 β -epimers, there are obtained 17 α -ethyl-7 α -methyl-11-keto-19-nortestosterone, 17 α -ethinyl-7 α -methyl-11-keto-19-nortestosterone, 7 α -methyl-17 α -propyl-11-keto-19-nortestosterone, 7 α -methyl-17 α -butyl-11-keto-19-nortestosterone, and 7 α -methyl-17 α -allyl-11-keto-19-nortestosterone, respectively.

EXAMPLE 33.

7 α -methyl-11 α -hydroxy-19-norandrostene-3,17-dione.

Using the procedure described in Example 30, but replacing 7 α ,17 α -dimethyl-19-nortestosterone by 7 α -methyl-19-norandrostene-3,17-dione, there is obtained 7 α -methyl-11 α -hydroxy-19-norandrostene-3,17-dione.

EXAMPLE 34.

7 α -methyl-11 β -hydroxy-19-norandrostene-3,17-dione.

Using the procedure described in Example 31, but replacing 7 α ,17 α -dimethyl-19-nortestosterone by 7 α -methyl-19-norandrostene-3,17-dione, there is obtained 7 α -methyl-11 β -hydroxy-19-norandrostene-3,17-dione.

EXAMPLE 35.

7 α -methyl-11 β -hydroxy-19-nortestosterone.

Using the procedure described in Example 31, but replacing 7 α ,17 α -dimethyl-19-nortestosterone by 7 α -methyl-19-nortestosterone, there is obtained 7 α -methyl-11 β -hydroxy-19-nortestosterone.

EXAMPLE 36.

7 α -methyl-11 α -hydroxy-19-nortestosterone.

Using the procedure described in Example 30, but replacing 7 α ,17 α -dimethyl-19-nortestosterone by 7 α -methyl-19-nortestosterone, there is obtained 7 α -methyl-11 α -hydroxy-19-nortestosterone.

EXAMPLE 37.

7 α -methyl-11 β -hydroxy-19-norandrostene-3,17-dione.

A solution of 1.6 g. of 7 α -methyl-11 β -hydroxy-19-nortestosterone in a mixture of 35 ml. of toluene and 15 ml. of cyclohexanone is heated until about 10 ml. are distilled to dry the solution. To the dry solution so obtained is added 1.5 g. of aluminum tertiary butoxide and the resulting solution is refluxed until the reaction is complete. An excess of a saturated aqueous solution of sodium potassium tartrate is added and the solvents are then removed by steam distillation. The residue is extracted with methylene chloride and the methylene chloride extract is dried and chromatographed on a magnesium silicate (Florisil) column. The column is developed with Skellysolve B hexanes containing increasing proportions of acetone and those fractions which, by paper chromatogram analysis, are shown to contain the desired 7 α -methyl-11 β -hydroxy-19-norandrostene-3,17-dione, are combined and evaporated to dryness. The residue is recrystallized from aqueous acetone. There is thus obtained 7 α -methyl-11 β -hydroxy-19-norandrostene-3,17-dione in the form of a crystalline solid.

Using the above procedure, but replacing 7 α -methyl-11 β -hydroxy-19-nortestosterone by 7 α -methyl-11 α -hydroxy-19-nortestosterone, there is obtained 7 α -methyl-11 α -hydroxy-19-norandrostene-3,17-dione.

EXAMPLE 38.

7 α -methyl-11 β -hydroxy-19-norandrostene-3,17-dione 3-pyrrolidinyl enamine.

Using the procedure described in Example 26, but replacing 7 α -methyl-19-norandrostene-3,17-dione by 7 α -methyl-11 β -hydroxy-19-norandrostene-3,17-dione, there is obtained the 3-pyrrolidinyl enamine of 7 α -methyl-11 β -hydroxy-19-norandrostene-3,17-dione.

Similarly, using the procedure of Example 26, but replacing 7 α -methyl-19-norandrostene-3,17-dione by 7 α -methyl-11 α -hydroxy-19-norandrostene-3,17-dione, there is obtained the 3-pyrrolidinyl enamine of 7 α -methyl-11 α -hydroxy-19-norandrostene-3,17-dione.

EXAMPLE 39.

7 α -methyl-17 α -ethinyl-11 β -hydroxy-19-nortestosterone.

Using the procedure described in Example 27, but replacing the 3-pyrrolidyl enamine of 7 α -methyl-19-norandrostene-3,17-dione by the 3-pyrrolidyl enamine of 7 α -methyl-11 β -hydroxy-19-norandrostene-3,17-dione, there is obtained 7 α -methyl-17 α -ethinyl-11 β -hydroxy-19-nortestosterone in the form of a crystalline solid.

Similarly, using the procedure of Example 27, but replacing the 3-pyrrolidyl enamine of 7 α -methyl-19-norandrostene-3,17-dione by the 3-pyrrolidyl enamine of 7 α -methyl-11 α -hydroxy-19-norandrostene-3,17-dione, there is obtained 7 α -methyl-17 α -ethinyl-11 α -hydroxy-19-nortestosterone.

EXAMPLE 40.

7 α ,17 α -dimethyl-11 β -hydroxy-19-nortestosterone.

Using the procedure described in Example 33, but replacing the 3-pyrrolidyl enamine of 7 α -methyl-19-norandrostene-3,17-dione by the 3-pyrrolidyl enamine of 7 α -methyl-11 β -hydroxy-19-norandrostene-3,17-dione, there is obtained 7 α ,17 α -dimethyl-11 β -hydroxy-19-nortestosterone in the form of a crystalline solid.

Similarly, using the procedure described in Example 29, but replacing the 3-pyrrolidyl enamine of 7 α -methyl-19-norandrostene-3,17-dione by the 3-pyrrolidyl enamine of 7 α -methyl-11 α -hydroxy-19-norandrostene-3,17-dione, there is obtained 7 α ,17 α -dimethyl-11 α -hydroxy-19-nortestosterone in the form of a crystalline solid.

EXAMPLE 41.

7 α -methyl-17 α -ethinyl-19-nortestosterone 17-acetate.

A mixture of 1 g. of 7 α -methyl-17 α -ethinyl-19-nortestosterone, 20 ml. of acetic anhydride and 1 ml. of pyridine is stirred and heated at 140° C. for 1 hour under a nitrogen atmosphere. The reaction mixture is then cooled to room temperature and stirred with 100 ml. of water for 2 hours. The product which separates is isolated by filtration. This product is a mixture of the desired 7 α -methyl-17 α -ethinyl-19-nortestosterone 17-acetate and the corresponding 3-enol 3,17-diacetate and the latter compound is hydrolyzed to the desired compound by heating the above product under reflux for 1 hr. with 100 ml. of methanol containing 2 ml. of concentrated hydrochloric acid. The reaction product so obtained is diluted with water and extracted with ether. The ether extract is dried over anhydrous magnesium sulfate and evaporated to dryness. The residue is dissolved in methylene chloride and chromatographed on a column of magnesium silicate (Florisil). The column is eluted with Skellysolve B containing increasing proportions of acetone and the fraction of the eluate, which is shown by paper chromatogram analysis to contain the desired product, is evaporated to dryness. The solid so obtained is recrystallized from aqueous methanol. There is thus obtained 7 α -methyl-17 α -ethinyl-19-nortestosterone 17-acetate in the form of a crystalline solid.

Similarly, by reacting 7 α -methyl-17 α -ethinyl-19-nortestosterone with the appropriate hydrocarbon carboxylic acid anhydride, for example, at temperatures between about 80° C. and 150° C. using the above procedure there are produced other 17-acylates thereof such as the 17-propionate, 17-butyrate, 17-valerate, 17-hexanoate, 17-trimethylacetate, 17-isobutyrate, 17-isovalerate, 17-cyclohexanecarboxylate, 17-cyclopentylpropionate, 17-p-hexyloxypropionate, 17-benzoate, 17-hemisuccinate, 17-phenylacetate, 17-acrylate, 17-crotonate, 17-undecylenate, 17-propionate, 17-cinnamate, 17-maleate, and 17-citraconate.

Similarly, by reacting other 7 α -methyl-19-nortestosterones and 7 α -methyl-17 α -(lower aliphatic hydrocarbon substituted)-19-nortestosterones with the appropriate hydrocarbon carboxylic acid anhydride using the above procedure there are obtained the corresponding 17-acylates such as 7 α -methyl-19-nortestosterone 17-propionate, 11-keto-7 α -methyl-19-nortestosterone 17-cyclopentylpropionate, 11 α -butyrox-

- 7 α -methyl-19-nortestosterone 17-butyrate, 7 α ,17 α -dimethyl-19-nortestosterone 17-acetate, 7 α -methyl-17 α -ethyl-19-nortestosterone 17-propionate, 11-keto-7 α -methyl-17 α -ethynyl-19-nortestosterone 17-acetate, 7 α -methyl-17 α -propyl-19-nortestosterone 17-acetate, 7 α -methyl-17 α -isopropyl-19-nortestosterone 17-propionate, 7 α -methyl-17 α -butyl-19-nortestosterone 17-valerate, 7 α -methyl-17 α -(α -methallyl)-19-nortestosterone 17-acetate, 11 α -acetoxy-7 α -methyl-17 α -isopropyl-19-nortestosterone 17-acetate, 11 α -propionyloxy-7 α -methyl-17 α -ethyl-19-nortestosterone 17-propionate, 11 α -acetoxy-7 α -methyl-17 α -allyl-19-nortestosterone 17-acetate, 11 β -hydroxy-7 α -methyl-17 α -isopropyl-19-nortestosterone 17-propionate, 11 β -hydroxy-7 α -methyl-17 α -isobutyl-19-nortestosterone 17-acetate, and 11 β -hydroxy-7 α -methyl-17 α -allyl-19-nortestosterone 17-isobutyrate.

EXAMPLE 42.

7 α -methyl-17 α -ethylnortestosterone.A. 7 α -methylandrostene-3,17-dione.

- To a solution of 20 g. of sodium dichromate dihydrate in 200 ml. of acetic acid was added 20 g. of 7 α -methyltestosterone with stirring and cooling in a cold water bath. The reaction mixture was allowed to stand for several hours and was then poured into ca. 1 litre of water. The precipitate so formed was isolated by filtration, washed with water and dried. The material (18.7 g.; m.p. 186 to 191° C.) so obtained was recrystallized from a mixture of acetone and Skellysolve B. There was thus obtained 15.6 g. of 7 α -methylandrostene-3,17-dione in the form of a crystalline solid having a melting point of 194 to 196° C.; [α]_D +196° (chloroform). The ultraviolet spectrum of the compound (in solution in ethanol) exhibited a maximum at 241 millimicrons (ϵ = 17,250).

- Anal.: Calcd. for C₂₀H₂₈O₂: C, 79.95; H, 9.39
Found: C, 79.81; H, 9.33:

B. 7 α -methyl-17 α -ethynyltestosterone.

- The 7 α -methylandrostene-3,17-dione (15.6 g.), obtained as described above, was dissolved in the minimum amount of boiling methanol with nitrogen bubbling through and 10 ml. of pyrrolidine was added. The mixture was cooled and the solid which had separated was isolated by filtration, washed with fresh methanol and ether and dried for about 15 minutes at 60° C. There was thus obtained the 3-pyrrolidyl enamine of 7 α -methylandrostene-3,17-dione in the form of a crystalline solid having a melting point of 199 to 205° C. with decomposition; [α]_D -190- (pyridine). The ultraviolet spectrum of the compound (in solution in ether) exhibited a maximum at 282 millimicrons (ϵ = 29,900).

- Anal.: Calcd. for C₂₁H₃₃NO: C, 81.53; H, 9.98; N, 3.95
Found: C, 81.57; H, 9.76; N, 3.77.

- While the above enamine was being dried, 25 ml. of a suspension (0.2 g./ml.) of sodium acetylide in xylene was centrifuged. The solid so isolated was suspended in 160 ml. of redistilled dimethylsulphoxide. To this suspension was added a slurry of the whole of the above enamine in 100 ml. of dimethylsulphoxide. The reaction mixture was stirred under an atmosphere of nitrogen for 3 hr. after which time 30 ml. of water and 50 ml. of methanol were added. The resulting mixture was heated to 50 to 60° C. for 1 hr. and was then stirred overnight at room temperature. The reaction mixture was then diluted with water and extracted with three 100 ml. portions of methylene chloride. The methylene chloride extracts were combined, washed with dilute hydrochloric acid and with water and then evaporated to dryness to give 2 g. of material. The aqueous washings from the above extraction were combined and made basic by the addition of sodium hydroxide solution. The solution so obtained was extracted several times with methylene chloride and the combined methylene chloride extracts were washed successively with dilute hydrochloric acid, dilute sodium carbonate and water before being dried over anhydrous sodium sulphate. The dried solution was filtered and the filtrate was evaporated to dryness. The residue (3.9 g.) was combined with the 2 g. of material obtained as described above and an acetone solution of the combined material was treated with a mixture of decolorizing charcoal (Darco), diatomaceous earth (Celite) and magnesium silicate (Florisil). The mixture was filtered and the filtrate was evaporated to dryness. The residue was recrystallized from a mixture of acetone and hexanes (Skellysolve B). There was thus obtained 3.9 g. of 7 α -methyl-17 α -ethynyltestosterone in

were combined, washed with dilute hydrochloric acid and with water and then evaporated to dryness to give 2 g. of material. The aqueous washings from the above extraction were combined and made basic by the addition of sodium hydroxide solution. The solution so obtained was extracted several times with methylene chloride and the combined methylene chloride extracts were washed successively with dilute hydrochloric acid, dilute sodium carbonate and water before being dried over anhydrous sodium sulphate. The dried solution was filtered and the filtrate was evaporated to dryness. The residue (3.9 g.) was combined with the 2 g. of material obtained as described above and an acetone solution of the combined material was treated with a mixture of decolorizing charcoal (Darco), diatomaceous earth (Celite) and magnesium silicate (Florisil). The mixture was filtered and the filtrate was evaporated to dryness. The residue was recrystallized from a mixture of acetone and hexanes (Skellysolve B). There was thus obtained 3.9 g. of 7 α -methyl-17 α -ethynyltestosterone in the form of a crystalline solid having a melting point of 190 to 192.5° C. An analytical sample having a melting point of 191 to 193° C. and $[\alpha]_D + 41^\circ$ (chloroform) was prepared by recrystallization from ethyl acetate. The ultraviolet spectrum of the compound (in solution in ethanol) exhibited a maximum at 242 millimicrons ($\epsilon = 16,550$).

Anal.: Calcd. for $C_{22}H_{30}O_2$: C, 80.93; H, 9.26
 Found: C, 80.86; H, 9.33.

EXAMPLE 45.

7 α -methyl-17 α -(1-propynyl)testosterone.

Using the procedure described in Example 44, Part B, but substituting sodium methylacetylide for sodium acetylide, there is obtained 7 α -methyl-17 α -(1-propynyl)-testosterone in the form of a crystalline solid.

EXAMPLE 46.

7 α -methyl-17 α -(1-butyryl)testosterone.

Using the procedure described in Example 44, Part B, but substituting sodium ethylacetylide for sodium acetylide, there is obtained 7 α -methyl-17 α -(1-butyryl)-testosterone in the form of a crystalline solid.

EXAMPLE 47.

7 α -methyl-17 α -ethynyltestosterone 17-propionate.

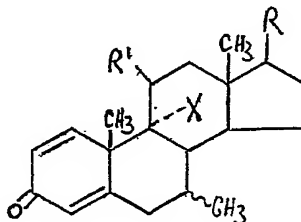
To a solution of 5 g. of 7 α -methyl-17 α -ethynyltestosterone in 20 ml. of pyridine is added 5 ml. of propionic anhydride. The resulting solution is refluxed under nitrogen until the hydroxyl absorption in the infrared region is gone, before being diluted with crushed ice and water. The solid which separates is isolated by filtration and recrystallized from aqueous acetone. There is thus obtained 7 α -methyl-17 α -ethynyltestosterone 17-propionate in the form of a crystalline solid.

Using the above procedure, but replacing propionic anhydride by the appropriate hydrocarbon carboxylic acid anhydride, there are obtained other 17-acylates of 7 α -methyl-17 α -ethynyltestosterone such as the 17-acetate, 17-butyrate, 17-valerate, 17-hexanoate, 17-trimethylacetate, 17-isobutyrate, 17-isovalerate, 17-cyclohexanecarboxylate, 17 β -cyclopentylpropionate, 17-p-hexyloxyphenylpropionate, 17-benzoate, 17-hemisuccinate, 17-phenylacetate, 17-acrylate, 17-crotonate, 17-undecylenate, 17-propiolate, 17-cinnamate, 17-maleate, and 17-citaconate.

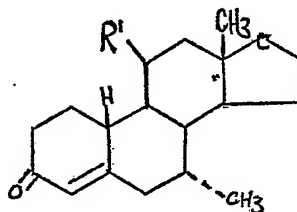
Similarly, by reacting other 7 α -methyl-17 α -alkynyltestosterones with the appropriate hydrocarbon carboxylic acid anhydride under the conditions shown in Example 4, there are obtained the corresponding 17-acylates such as 7 α -methyl-17 α -(1-propynyl)-testosterone 17-acetate, 7 α -methyl-17 α -(1-propynyl)testosterone 17-propionate, 7 α -methyl-17 α -(1-propynyl)testosterone 17-isobutyrate, 7 α -methyl-17 α -(1-propynyl)-testosterone 17 β -cyclopentylpropionate, 7 α -methyl-17 α -(1-butyryl)testosterone 17-acetate, 7 α -methyl-17 α -(1-butyryl)testosterone 17-propionate, and 7 α -methyl-17 α -(1-butyryl)testosterone 17 β -cyclopentylpropionate.

WHAT WE CLAIM IS:—

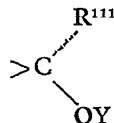
1. A 7-methyltestosterone selected from compounds having the formulae:



and

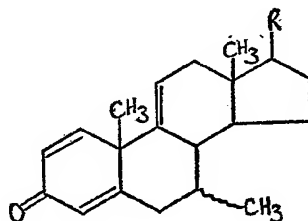


wherein R¹ is hydrogen, α - or β -hydroxy, α -acyloxy, or keto, R is β -hydroxy, α -methyl- β -hydroxy, α -methyl- β -acyloxy or β -acyloxy, X is hydrogen, fluorine, chlorine, bromine or iodine, and C is $>C=O$ or



wherein R¹¹ is hydrogen or a lower aliphatic hydrocarbon radical and Y is hydrogen or acyl, wherein the acyl radical is that of a hydrocarbon carboxylic acid containing from 1 to 12 carbon atoms.

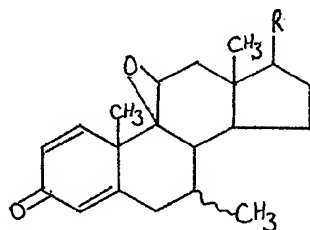
2. 1-dehydro-7,17-dimethyltestosterone.
3. 1-dehydro-7 α ,17-dimethyltestosterone.
4. 7 α -methyl-19-nortestosterone acetate.
5. 7 α -methyl-19-nortestosterone.
6. 7 α -methyl-19-norandrostene-3,17-dione.
7. 7 α ,17 α -dimethyl-19-nortestosterone.
8. 7 α -methyl-17 α -ethyl-19-nortestosterone.
9. 7 α -methyl-17 α -ethinyl-19-nortestosterone.
10. 7 α -methyl-17 α -ethinyl-19-nortestosterone 17-acetate.
11. A 7-methyl-9(11)-dehydrotestosterone represented by the formula:



wherein R is a 17-substituent selected from β -hydroxy, α -methyl- β -hydroxy, α -methyl- β -acyloxy and β -acyloxy wherein the acyl radical of the acyloxy group is that of a hydrocarbon carboxylic acid containing from one to twelve carbon atoms, inclusive.

12. A 7-methyl-9 β ,11 β -epoxytestosterone represented by the formula:

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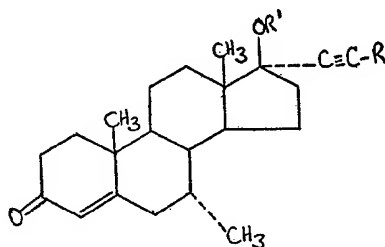
wherein R is a 17-substituent selected from β -hydroxy, α -methyl- β -hydroxy, α -methyl- β -acyloxy and β -acyloxy wherein the acyl radical of the acyloxy group is that of a hydrocarbon carboxylic acid containing from one to twelve carbon atoms, inclusive.

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13. 1-dehydro-7,17-dimethyl-9 α -fluoro-11 β -hydroxytestosterone.

14. A 7 α -methyl-17 α -alkynyltestosterone having the formula:

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wherein R is selected from the class consisting of hydrogen, methyl, and ethyl, and R¹ is selected from the group consisting of hydrogen and acyl wherein the acyl radical is that of a hydrocarbon carboxylic acid containing from 1 to 12 carbon atoms, inclusive.

15

15. 7 α -methyl-17 α -ethynyltestosterone.

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16. 7 α -methyl-17 α -ethynyltestosterone propionate.

17. 7 α -methyl-17 α -ethyltestosterone and 17-acylates thereof wherein the acyl radical is that of a hydrocarbon carboxylic acid containing from 1 to 12 carbon atoms inclusive.

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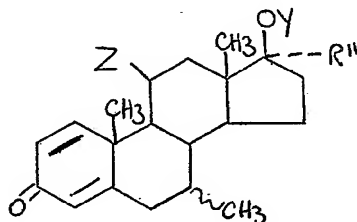
18. A 7 α -methyl-19-nortestosterone 17-acylate wherein the acyl group is that of a hydrocarbon carboxylic acid containing from 1 to 12 carbon atoms, inclusive.

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19. 7 α -methyl-19-nortestosterone 17-propionate.

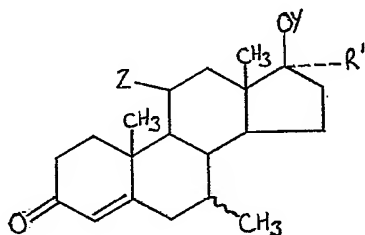
20. A process for the preparation of a 1-dehydro-7-methyltestosterone having the general formula:—

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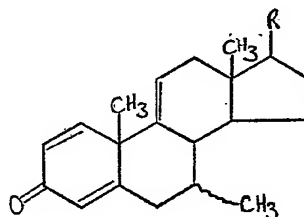
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wherein R¹¹ is hydrogen or lower alkyl, Y is hydrogen or the acyl radical of an organic carboxylic acid and Z is hydrogen, a 9,11-double bond or a keto, alpha or beta hydroxy or alpha-acyloxy group which comprises subjecting a compound having the general formula:—



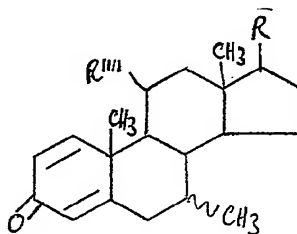
wherein R¹¹, Y and Z are as above defined to 1-dehydrogenation by known methods.

21. A process for the preparation of a compound having the general formula:—



- 5 wherein R is a 17-substituent selected from beta-hydroxy, alpha-methyl-beta-hydroxy, alpha-methyl-beta-acyloxy and beta-acyloxy wherein the acyl radical of the acyloxy group is that of a hydrocarbon carboxylic acid containing from 1 to 12 carbon atoms inclusive which comprises dehydrating a steroid having the general formula:—

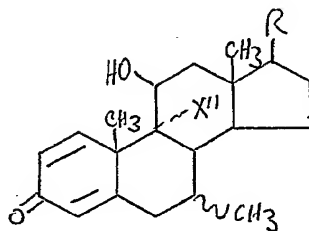
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- 10 wherein R¹¹¹¹ is an alpha-hydroxy or beta-hydroxy and R is as above defined.

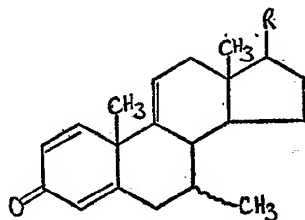
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22. A process for the preparation of a compound having the general formula:—



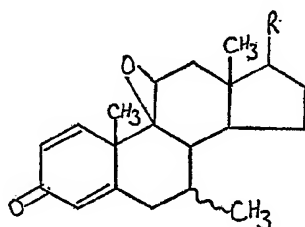
- 15 wherein R is beta-hydroxy, alpha-methyl-beta-hydroxy, alpha-methyl-beta-acyloxy or beta-acyloxy wherein the acyl radical of the acyloxy group is that of a hydrocarbon carboxylic acid containing from 1 to 12 carbon atoms inclusive and X¹¹ is chlorine, bromine or iodine which comprises treating a compound having the general formula:—

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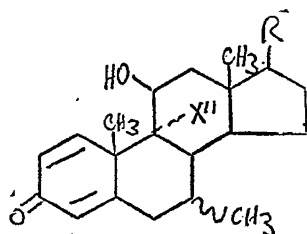


wherein R is as above defined with a hypohalous acid in which the halogen is chlorine, bromine or iodine.

23. A process for the preparation of a compound having the general formula:—

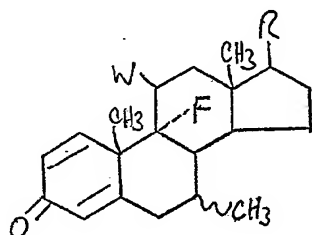


wherein R is a 17-substituent selected from beta-hydroxy, alpha-methyl-beta-hydroxy, alpha-methyl-beta-acyloxy and alpha-acyloxy wherein the acyl radical of the acyloxy group is that of a hydrocarbon carboxylic acid containing from 1 to 12 carbon atoms inclusive which comprises treating a compound having the general formula:—



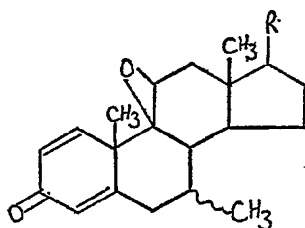
wherein X¹¹ is bromine, chlorine or iodine and R is as above defined with a weak base.

24. A process for the preparation of a compound having the general formula:—



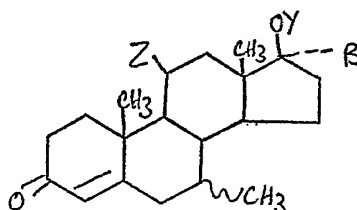
wherein W represents a hydroxy or keto group and R represents beta-hydroxy, alpha-methyl-beta-hydroxy, alpha-methyl-beta-acyloxy or alpha-acyloxy wherein the acyl radical of the acyloxy group is that of a hydrocarbon carboxylic acid containing from

1 to 12 carbon atoms inclusive which comprises treating a compound having the general formula: —

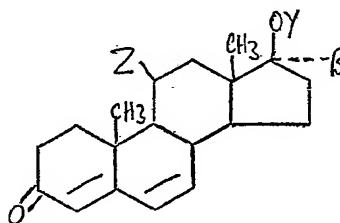


5 wherein R is as above defined with hydrofluoric acid and then if desired oxidising to produce the corresponding 11-keto derivative. 5

25. A process for the preparation of a 7-methyltestosterone having the general formula: —

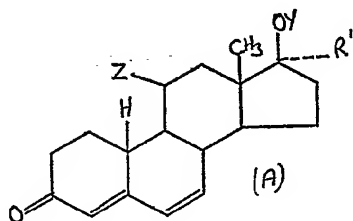


10 wherein B represents a lower-alkyl radical other than a methyl, Y is hydrogen or the acyl radical of an organic carboxylic acid and Z is hydrogen, a 9,11-double bond, keto, alpha or beta-hydroxy or alpha-acyloxy which comprises reacting a compound having the general formula: — 10

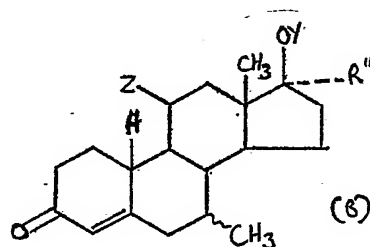


15 wherein B, Y and Z are as above defined with a methyl Grignard reagent in the presence of an agent which suppresses 1,2-addition of the Grignard reagent to obtain the desired compound. 15

26. A process for the preparation of a 7-methyltestosterone which comprises reacting a compound having the formula:

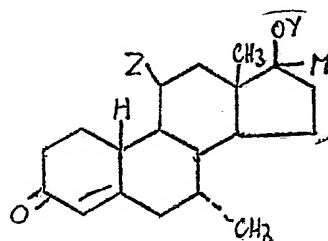


wherein R^{11} is hydrogen or lower-alkyl, Y is hydrogen or the acyl radical of an organic carboxylic acid, and Z is hydrogen, a 9(11)-double bond, keto, α - or β -hydroxy, or α -acyloxy, with a methyl Grignard reagent in the presence of an agent which suppresses 1,2-addition of the Grignard reagent to obtain a compound having the formula:

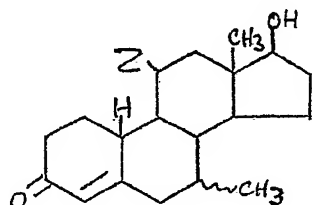


wherein R^{11} , Y, and Z have the significance above defined and if desired in the case where Y is hydrogen acylating to produce the corresponding 17-acylate.

27. A process for the preparation of a compound having the general formula:—

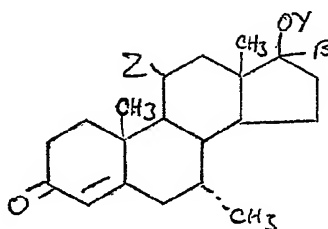


wherein Z is hydrogen, a 9,11-double bond, keto, alpha or beta-hydroxy or alpha-acyloxy, Y is hydrogen or the acyl radical of an organic carboxylic acid and M is an alkyl, alkenyl or alkynyl group which comprises subjecting a compound having the general formula:—



wherein Z is as above defined to oxidation to produce the corresponding 7-methyl-17-ketosteroid, converting the latter compound to the corresponding 3-enamine, treating the 3-enamine with an alkylmagnesium halide, an alkenylmagnesium halide, an alkynylmagnesium halide, an alkyllithium, an alkenyllithium or an alkali metal derivative of an alkyne, hydrolysing the 3-enamine of the 7alpha-methyl-17-alkylated steroid so obtained and then if desired acylating to produce the corresponding 17-acyloxy derivative.

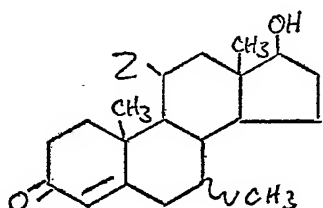
28. A process for the preparation of a compound having the general formula:—



wherein Z is hydrogen, a 9,11-double bond, keto, alpha or beta-hydroxy or alpha-acyloxy, Y is hydrogen or the acyl radical of an organic carboxylic acid and B is an alkenyl or alkynyl group or an alkyl group other than methyl which comprises sub-

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wherein Z is as above defined to oxidation to produce the corresponding 7-methyl-17-keto steroid, converting the latter compound to the corresponding 3-enamine, treating the 3-enamine with an alkylmagnesium halide, an alkenylmagnesium halide, an alkynylmagnesium halide, an alkyl lithium, an alkynyl lithium or an alkali metal derivative of an alkyne, hydrolysing the 3-enamine of the 7alpha-methyl-17-alkylated steroid so obtained and then if desired acylating to produce the corresponding 17-acyloxy derivative.

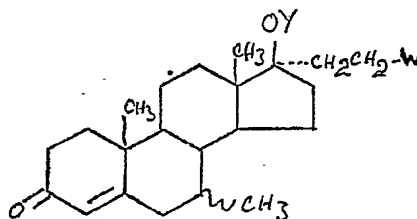
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29. A compound having the general formula: —

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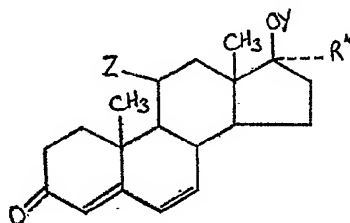
wherein Y is hydrogen or acyl wherein the acyl radical is that of a hydrocarbon carboxylic acid containing from 1 to 12 carbon atoms inclusive and W represents methyl or ethyl.

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30. A process which comprises reacting 6-dehydro-19-nortestosterone with a methyl Grignard reagent in the presence of an agent which suppresses 1,2-addition of the Grignard reagent to obtain 7alpha-methyl-19-nortestosterone and, if desired, acylating the latter compound by reaction with a hydrocarbon carboxylic acid anhydride or halide to obtain the corresponding 7alpha-methyl-19-nortestosterone 17-acylate.

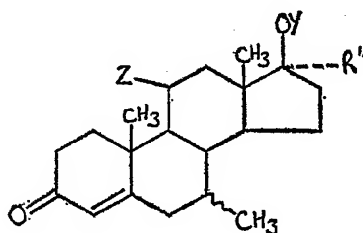
31. A process which comprises the steps of reacting a 6-dehydrotestosterone having the formula:



5 wherein R^{11} is hydrogen or lower-alkyl, Y is hydrogen or the acyl radical of an organic carboxylic acid, and Z is hydrogen, a 9(11)-double bond, keto, α - or β -hydroxy, or α -acyloxy, wherein the acyl of the acyloxy group is the acyl radical of an organic carboxylic acid, with a methyl Grignard reagent in the presence of an agent which suppresses 1,2-addition of the Grignard reagent to obtain a 7-methyltestosterone having the formula:

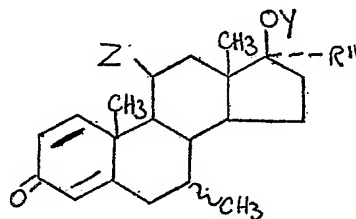
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wherein R^{11} , Y, and Z have the significance hereinbefore defined and subjecting the latter compound to 1-dehydrogenation by known methods to obtain a compound having the formula:



15 wherein R^{11} , Y and Z have the significance above defined.

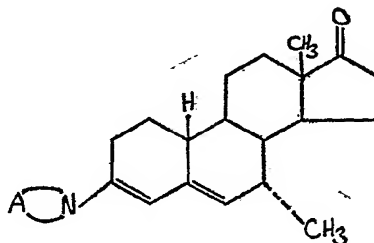
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32. A process which comprises reacting 6-dehydrotestosterone with a methyl Grignard reagent in the presence of an agent which suppresses 1,2-addition of the Grignard reagent to obtain 7-methyltestosterone and subjecting the latter compound to 1-dehydrogenation by known methods to obtain 1-dehydro-7-methyltestosterone.

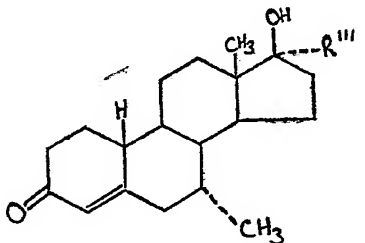
20 33. A process which comprises reacting 6-dehydro-17-methyltestosterone with a methyl Grignard reagent in the presence of an agent which suppresses 1,2-addition of the Grignard reagent to obtain 7,17-dimethyltestosterone and subjecting the latter compound to 1-dehydrogenation by known methods to obtain 1-dehydro-7,17-dimethyltestosterone.

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34. A process which comprises reacting a 3-enamine of 7 α -methylnorandrostene-3,17-dione having the formula:



5 wherein A is an alkylene group which, together with the attached nitrogen atom, forms a ring containing from 5 to 6 members, inclusive, with an alkylating agent selected from the group consisting of alkylmagnesium halides, alkenylmagnesium halides, alkynylmagnesium halides, alkyllithium, alkenyllithium, and alkali metal derivatives of alkynes, and hydrolyzing the thus obtained 3-enamine of the corresponding 7 α -methyl-17-alkylated-19-nortestosterone to produce a 7 α -methyl-17-alkylated-19-nortestosterone having the formula:



wherein R^{'''} is alkyl, alkenyl, or alkynyl, and, if desired, reacting the compound so obtained with an acylating agent to produce the corresponding 17-acylate.

15 35. A process as claimed in claim 34 wherein the alkylating agent is a methylmagnesium halide whereby there is produced 7 α ,17-dimethyl-19-nortestosterone and the corresponding 17-acylate.

36. A process as claimed in claim 34 wherein the alkylating agent is an alkali metal acetylide whereby there is produced 7 α -methyl-17-ethynyl-19-nortestosterone.

20 37. A process as claimed in claim 34 which includes the additional step of subjecting the 7 α -methyl-17-alkylated-19-nortestosterone to microbiological 11-hydroxylation to obtain the corresponding 7 α -methyl-17-alkylated-11-hydroxy-19-nortestosterone.

25 38. A process which comprises the steps of subjecting 7 α -methyl-19-norandrostene-3,17-dione to microbiological 11-hydroxylation to obtain the corresponding 7 α -methyl-11-hydroxy-19-norandrostene-3,17-dione, converting the latter compound to the corresponding 3-enamine, reacting the 3-enamine with an alkylating agent selected from the group consisting of alkylmagnesium halides, alkenylmagnesium halides, alkynylmagnesium halides, alkyllithium, alkenyllithium, and alkali metal derivatives of alkynes, and hydrolyzing the thus obtained 3-enamine of the corresponding 7 α -methyl-17-alkylated-11-hydroxy-19-nortestosterone to produce the corresponding 7 α -methyl-17-alkylated-11-hydroxy-19-nortestosterone.

30 39. A process which comprises reacting a 3-enamine of 7 α -methylandrostene-3,17-dione with an alkali metal acetylide and hydrolyzing the 3-enamine of 7 α -methyl-17 α -ethynyltestosterone so obtained to yield 7 α -methyl-17 α -ethynyltestosterone, and if desired, treating the latter compound with an acylating agent to obtain the corresponding 17-acylate wherein the acyl radical is that of a hydrocarbon carboxylic acid.

35 40. A process which comprises catalytically hydrogenating 7 α -methyl-17 α -ethynyltestosterone or the 17-acylate thereof wherein the acyl radical is that of a hydrocarbon carboxylic acid, to obtain 7 α -methyl-17 α -ethyltestosterone or the corresponding 17-acylate thereof.

41. The process of claim 40 wherein the hydrogenation is carried out in the presence of a palladium-on-charcoal catalyst.
42. A process for the preparation of a compound as claimed in any of claims 1 to 19 or 29 substantially as herein described.
- 5 43. A compound as claimed in any of claims 1 to 19 or 29 when prepared by a process as claimed in any of claims 20 to 28 or 30 to 42. 5
44. A pharmaceutical composition comprising as the active ingredient a compound as claimed in any of claims 1 to 19 or 29 together with a pharmaceutically acceptable carrier.

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Leamington Spa: Printed for Her Majesty's Stationery Office, by the Courier Press
(Leamington) Ltd.—1963. Published by The Patent Office, 25 Southampton Buildings,
London, W.C.2, from which copies may be obtained.